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A few publications dated 1959 but received too late for inclusion in "Medical Genetics 1959" have been reviewed here. The organization is essentially the same as that of "Medical Genetics 1958" (J. Chron. Dis. 10:255-363, 1959) and "Medical Genetics 1959" (J. Chron. Dis. 12:1-202, 1960). The sections referred to by paragraph numbers 1 through 293 are those in "Medical Genetics 1958"; paragraph numbers 294 through 643 indicate those in "Medical Genetics 1959"; paragraph numbers 644 through 950 are in this issue. The illustrations and tables have been numbered beginning with Fig. 28 and Table XIII to follow consecutively the twenty-seven figures and twelve tables which appeared in "Medical Genetics 1959."

At the suggestion of Prof. Curt Stern, in "Medical Genetics 1960" each bibliographic reference is provided with the number of the section in which it is mentioned.

Reprints of articles for review in the future should be sent to Dr. Victor A. McKusick, Johns Hopkins Hospital, Baltimore 5, Md.

I. NEW BOOKS, SYMPOSIA, AND CONGRESSES

Books: 644. Bell, P. R., editor: Darwin's Biological Work: Some Aspects Reconsidered, London, 1959, Cambridge University Press.

As indicated by the title, selected aspects of Darwin's biologic work are reconsidered in the light of developments in the specific areas since Darwin. Haldane gives a valuable discussion of natural selection beginning with sketches of Darwin's opinions and of genetics.

645. Falconer, D. S.: Introduction to Quantitative Genetics, New York, 1960, The Ronald Press Company.

The author works in the Agricultural Research Council's Unit of Animal Genetics at the University of Edinburgh. In the preface he states, "My aim in writing this book has been to provide an introductory textbook of quantitative genetics, with the emphasis on general principles rather than on practical application, and one moreover that can be understood by biologists of no more than ordinary mathematical ability. In pursuit of this latter aim I have set out the mathematics in the form that I, being little of a mathematician, find most comprehensible. . . ."

Topics discussed include gene frequencies, the effects of migration, mutation, and selection, resemblance between relatives, effects of inbreeding, and others.

646. Fuller, J. L., and Thompson, W. R.: Behavior Genetics, New York, 1960, John Wiley & Sons, Inc.

Fuller is senior staff scientist and assistant director at the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine. Thompson is professor of psychology at Wesleyan University.

Fully one-third of the monograph is devoted to general principles of genetics, experimental methods in behavior genetics, and methods in human genetics, particularly human behavior genetics. This feature of the book will undoubtedly increase greatly its usefulness as a textbook and a reference book for those with little previous training in genetics.

Subsequent chapters of the book treat in a systematic manner those characteristics relating to the nervous system. The titles of these chapters are:

Variation in sensory and perceptual processes
Response processes
Intellectual abilities
Personality and temperament
Mental disorders
Heredity and individual differences in behavior

Extensive references and good author and subject indices are provided. The book provided a good review of an important but difficult area.

647. Gallup, G., and Hill, E.: The Secrets of Long Life, New York, 1960, Random House, Inc.

From about 29,000 Americans 95 years of age and older, the authors selected a sample of 402 for study. The longevity of close relatives was demonstrated in this study as in that of Raymond Pearl (*The Ancestry of the Long-Lived*, 1934). In the sample studied the following data were found:

LONGEVITY OF RELATIVES	PERCENTAGE
At least one parent lived to 90 years or older	26
At least one parent or one sibling lived to 90 or older	39
At least one parent lived to 80 or older	51
At least one parent or one sibling lived to 80 or older	73

The suspicion is stated that the record would have been more impressive if it were not for the "accidental deaths by disease" in an earlier era when tuberculosis, typhoid, diphtheria, pneumonia, and other infectious diseases were more prevalent. The evidence suggested that persons of northern European stock in the United States have a longer life expectancy than Americans of middle or southern European ancestry. Forty-one per cent of the sample were of British ancestry. The long-lived individuals of this sample came from large families with an average of about 6 children as compared with the national average of 3.6 children in the 1850's.

The report of the study is written in a popular vein. It gives mainly qualitative answers to the questions asked. No indication of the precise sampling technique used is provided in the publication. However, Gallup states in a personal communication that the procedure was as follows: An attempt to get a random, or probability, sample of all persons 95 years of age or older was made. A sample of communities stratified by area of the country, size, etc., was drawn. A representative then investigated newspaper files and talked to clergymen and others "to get as complete a list as possible of any or all who had reached the age of 95." A random sample of these names was then taken.

648. Gardner, E. J.: Principles of Genetics, New York, 1960, John Wiley & Sons, Inc.

This is a useful general text. The author has had enough contact with human genetics to give his book some orientation along that line but avoids the mistake of using an excessive amount of human material in an attempt to increase the interest of the student. Gardner, of Utah State University, is probably the only professor of genetics who has a clinical syndrome named for him. Gardner's syndrome (¶770) is colonic polyposis with characteristic osteomata of the jaw and other bones, multiple sebaceous cysts, and fibromata.

649. Garn, S. M.: Readings on Race, Springfield, Ill., 1960, Charles C Thomas, Publisher.

Garn, S. M.: Human Races, Springfield, Ill., 1961, Charles C Thomas, Publisher.

In 1950 Garn collaborated with Coon and Birdsell on a small volume on human races. They avoided the traditional anthropometrics and morphologic classifications and concentrated on how races come into existence. The rapid

developments of the last 10 years have more than justified their abandonment of the then prevalent view of the pure race capable of little change. *Human Races*, a companion for the source book *Readings on Race*, leans heavily on the techniques of biochemical genetics as applied to physical anthropology. The two books will undoubtedly prove highly useful for students of physical anthropology or human genetics.

650. Kalmus, H., and Hubbard, S. J.: The Chemical Senses in Health and Disease, Springfield, Ill., 1960, Charles C Thomas, Publisher.

What is known of the physiology, pathology, genetics, and other aspects of taste and smell is discussed.

651. Medawar, P. B.: The Future of Man. The BBC Reith Lectures, 1959, New York, 1960, Basic Books, Inc.

One of 1960's Nobel laureates discussed in this series of lectures many aspects of human biology, particularly the genetic ones.

652. Penrose, L. S., editor: Recent Advances in Human Genetics, London, 1961, J. & A. Churchill, Ltd.

The newest comer to the familiar Recent Advances Series is a collection of eight essays by persons who with a single exception have been associated with the Galton Laboratory at some time. The chapters are:

a. Penrose, L. S.: Mutation.
b. Harnden, D. G.: The Chromosomes.
c. Miller, O. J.: Developmental Sex Abnormalities.
d. Penrose, L. S.: Genetics of Growth and Development of the Fetus (Including a Consideration of Congenital Malformations).
e. Gerald, P. S.: The Abnormal Hemoglobins.
f. Holt, S. B.: Inheritance of Dermal Ridge Patterns.
g. Renwick, J. H.: Elucidation of Gene Order.
h. Smith, C. A. B.: Statistical Methods and Theory.

Much useful information and interpretation are provided by this collection of reviews.

653. Putnam, F. W., editor: The Plasma Proteins. Vol. 1. Isolation, Characterization, and Function. Vol. 2. Biosynthesis, Metabolism, and Alterations in Disease, New York and London, 1960, Academic Press, Inc.

Each chapter has some implication for medical genetics. A final chapter by Gitlin and Janeway is specifically entitled "Genetic Alterations in Plasma Proteins in Man."

654. Rife, D. C.: Heredity and Human Nature, New York, 1960, Vantage Press, Inc.

This is an elementary and at times superficial treatise on human genetics. Its coverage is broader than its title might suggest. No harm can come from recommending it to undergraduate students, who will undoubtedly be greatly informed by reading it.

655. Shettles, L. B.: Ovum Humanum, New York, 1960, Hafner Publishing Co., Inc.

The monograph presented a series of excellent photomicrographs of the human ovum studied by phase contrast technique. The whole sequence of growth and maturation of the ovum, its appearance in the Fallopian tube, and its nutrition were covered. Shettles added sperm to mature ova in tissue culture and observed development to the blastocyst stage.

Of particular interest to the geneticist is the demonstration of the polar bodies. He stated that the first polar body is formed shortly before ovulation. While the second may develop in the follicle, it usually is not produced until a spermatozoon has penetrated the secondary oocyte. The relevance of this is to timing the effect of maternal age in increasing the incidence of some presumably nondisjunctional states.

656. Stanbury, J. B., Wyngaarden, J. B., and Fredrickson, D. S., editors: The Metabolic Basis of Inherited Disease, New York, 1960, McGraw-Hill Book Company, Inc.

The editors and forty-three other contributing authors in 1,424 pages discuss in a comprehensive and up to date manner those genetic disorders about which there is reasonably detailed biochemical information. The first two chapters, which provide general discussion of matters such as pathogenetic mechanisms in genetic defects, the chemical nature of the genetic material, and the mechanisms of gene action, are well done. Thereafter, the following topics are discussed:

Diseases manifest primarily as disorders of carbohydrate metabolism
- Diabetes mellitus
- Pentosuria
- Fructosuria
- Glycogen deposition diseases
- Galactosemia
- Hyperbilirubinemia

Diseases primarily related to disorders of amino acid metabolism
- Familial goiter
- Phenylketonuria
- Tyrosinosis
- Alcaptonuria
- Albinism
- Primary hyperoxaluria and oxalosis
- Maple syrup urine disease

Diseases characterized by evidence of abnormal lipid metabolism (the lipidoses)
- Essential familial hyperlipidemia
- Infantile amaurotic family idiocy
- Niemann-Pick disease
- Gaucher's disease
- Disorders of steroid metabolism
- The adrenogenital syndrome

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Diseases of purine and pyrimidine metabolism
- Gout
- Xanthinuria
- Oroticaciduria
- Beta-aminoisobutyricaciduria

Diseases primarily manifest as abnormalities in metal metabolism
- Wilson's disease
- Hemochromatosis
- Periodic paralysis
- Adynamia episodica hereditaria
- Pseudohypoparathyroidism

Diseases of porphyrin metabolism
- The porphyrias

Diseases manifest primarily in the blood and the blood-forming tissues
- Hereditary spherocytosis
- Drug-induced hemolytic anemia (primaquine sensitivity)
- The hereditary methemoglobinemias
- The hemoglobinopathies and thalassemia
- The blood-clotting factors

Diseases manifest primarily in renal tubular transport
- Familial hypophosphatemia and vitamin D–resistant rickets
- The syndrome of osteomalacia, renal glycosuria, aminoaciduria, and hyperphosphaturia (the Fanconi syndrome)
- Renal glycosuria
- Renal tubular acidosis
- Vasopressin-resistant diabetes insipidus
- Glycinuria
- Cystinuria
- Hartnup disease

Diseases involving deficiency of circulating enzymes or plasma proteins
- Hypophosphatasia
- Hereditary hypoproteinemias and other plasma protein abnormalities
- Acatalasia

As an appendix, Yesley describes the methods of coding and filing family records used in the Department of Human Genetics, University of Michigan Medical School.

The quality of the individual contributions is uniformly excellent. The pedigree charts and line drawings have been done by a standardized technique, which adds to the attractiveness of the volume. The half-tone illustrations, especially the x-rays, are at times a bit unclear. "Dissimulation" is used when "dissimilation" is intended (p. 4). "Phenocopy" is used for both genetic and environmental facsimiles of a given genetic entity (p. 14). Goldschmidt (¶60) invented the term to refer to environmentally determined copies; "genetic mimic" or "genocopy" is perhaps the better term for the genetically determined

copy. "Pseudodominant" is used for the pedigree pattern resulting from the mating of a person homozygous for a recessive gene with one heterozygous for the gene (p. 69). "Quasidominant" is more satisfactory to the etymologist because mixing of Greek and Latin origins is avoided.

At least two of the conditions discussed in separate chapters have been observed in only one patient each: oroticaciduria (¶747) and tyrosinosis. That these are genetic is plausible and is supported, at least in the first instance, by the presence of parental consanguinity.

657. Stern, C.: Principles of Human Genetics, ed. 2, San Francisco, 1960, W. H. Freeman & Company.

At last the revision awaited for over 10 years has appeared. The organization and emphasis are the same as in the first edition, but extensive rewriting and considerable expansion have been necessary to incorporate the rapid developments in human genetics in the last decade. Our anticipations have been adequately satisfied.

A possible weakness is in the area of biochemical genetics and the chemistry of heredity. Desoxyribonucleic acid does not appear in the index. In the chapter on "Genic Action" or elsewhere, it would have been useful to have at least a brief résumé of the current dogma that genetic information is somehow coded in the sequence of purine and pyrimidine bases of DNA, that the primary function of the gene is to specify the amino acid sequence of proteins, that RNA is somehow involved in transfer of the code from its place of storage in the chromosome to the site of primary gene action, that is, protein synthesis, in the ribosomes of the cytoplasm, and that all characteristics of proteins are a logical result of the amino acid sequence. The studies of human hemoglobin are to a large extent responsible for development of the modern dogma.

Nevertheless, Stern's book is probably the best single text to recommend to the student of human genetics.

658. Strauss, B. S.: An Outline of Chemical Genetics, Philadelphia, 1960, W. B. Saunders Company.

The territory covered is much the same as that in Zamenhof's book (¶315) and in Anfinsen's book (¶294). However, the presentation is sufficiently novel that no serious duplication of effort has resulted. In fact, this book like the others deserves thorough reading and will reward careful study. The content is organized under the following main headings:

The genetic control of protein synthesis
The chemical nature of the hereditary material
The molecular meaning of genetic recombination
Mutation as a chemical process
Nucleocytoplasmic relationships and the problem of protein synthesis
The biochemical genetics of man

The monograph is a highly recommended exposition of the modern dogma of genetics and the evidence on which it is based.

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Symposia: 659. Sutton, H. E., editor: Genetic Information and the Control of Protein Structure and Function, Transactions of the First Conference on Genetics, Oct. 19 to 22, 1959, New York, 1960, Josiah Macy, Jr. Foundation.

This conference followed the pattern established by Fremont-Smith for other Macy conferences. Discussions on successive days were led by Watson (chromosomal structure and the coding mechanism), Ingram (genetic control of protein structure), and Spiegelman (factors modulating the biochemical expression of genetic systems). A useful feature is a summarization of each day's discussion by Lederberg, Bearn, and Wagner.

In the first chapter (first day) the chemical nature of DNA, the mechanics of replication, and the coding mechanism were covered. The mechanical fragility of the DNA molecule was emphasized. Precise statements about the size of the DNA molecule were considered difficult. In fact, the provocative suggestion was made that each chromosome may consist of a single DNA molecule, or two, since it is unknown what happens at the centromere (p. 47). Lederberg pointed out the great advantage which could accrue from availability of specific chemical reagents for each of the four simple bases in DNA (p. 61). Such "would be supremely valuable, not only for analytical purposes but also for attempting specific modifications in the structure of DNA."

The hemoglobins served in the second chapter as a useful basis for discussion of gene action in protein specification. The dogma that all properties of the protein are consequences of the amino acid sequence, determination of which is the primary role of genes, was discussed.

Factors influencing genetic expression at the biochemical level were discussed in the third chapter.

A small criticism is that the proceedings of the conference are difficult reading and that it is hard to find again a piece of information, a well-turned phrase, or a provocative idea which one reads in the proceedings. These, however, are difficulties with the published version of all the Macy conferences.

660. Blumberg, B. S., editor: Proceedings of Conference on Genetic Polymorphism and Geographic Variations in Disease, held in Bethesda Feb. 23 to 25, 1960, Washington, 1960, U. S. Public Health Service.

The content and presentation of these proceedings are highly worth while. After general discussions (Boyd, Gordon, Paul, and Lilienfeld), the symposium considered specific polymorphisms: blood groups (Reed), hemoglobins (Neel), haptoglobins and transferrins (Giblett), glucose-6-phosphate dehydrogenase deficiency of erythrocyte (Motulsky), and β-aminoisobutyricaciduria (Gartler). The discussions were illuminating and are well recorded in the proceedings.

661. Biological Effects of Radiation, Vol. 22 of Proceedings of the Second United Nations International Conference on the Peaceful Uses of Atomic Energy, held in Geneva Sept. 1 to 13, 1958, Geneva, 1960, United Nations.

The many papers of genetic significance included the following:

a. Ford, C. E., and Mole, R. H.: Chromosomes and Carcinogenesis. Observations on Radiation-Induced Leukaemias.

b. Nebel, B. R.: Fine Structure of Chromosomes in Man and Other Metazoa and Testicular Recovery From X-rays in Mammals.

c. Russell, W. L., and Russell, L. B.: Radiation-Induced Genetic Damage in Mice.

d. Tinyakov, G. G., and Arsenieva, M. A.: Cytogenetic Effect of Ionizing Radiation on Nuclei of Germ Cells of Monkeys.

e. Dubinin, N. P.: Mechanism of Radiation Effect on Heredity and the Problem of Radiosensitivity.

f. Grahn, D.: The Genetic Factor in Acute and Chronic Radiation Toxicity.

662. Structure and Function of Genetic Elements, Twelfth Brookhaven Symposium in Biology, held June 1 to 3, 1959.

Prompt publication was a distinct advantage. Participants were Doty, Rich, Sinsheimer (single-stranded DNA), Crick (the coding problem), Hoagland, Brown, Freese (the molecular explanation of mutation), Levinthal (alkaline phosphatase of *Escherichia coli*), Brenner, Luria, Steffenson, Weigle, Swift (nuclear fine structure by electron microscopy), and Woods.

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663. Gardner, L. I., editor: Molecular Genetics and Human Disease, symposium held in Syracuse April, 1959, Springfield, Ill., 1960, Charles C Thomas, Publisher.

Speakers and topics included Crick on DNA, Ingram on mutations and protein structure, Sidbury on galactosemia, Kirkman on primaquine sensitivity, Russell on mouse genetics, Polani on sex chromosome anomalies, Newcombe on data accumulation for estimating increased mutation rate, and Crowe on mutation and selection.

664. The Processes of Ongoing Human Evolution, *Human Biology*, February, 1960, Detroit, 1960, Wayne University Press.

Many aspects of importance and interest are covered. The contributions were as follows:

a. Baker, P. T.: Climate, Culture and Evolution.

b. Livingston, F. B.: Natural Selection, Disease, and Ongoing Human Evolution, as Illustrated by the ABO Blood Groups.

c. Motulsky, A. G.: Metabolic Polymorphisms and the Role of Infectious Diseases in Evolution.

d. Hulse, F. S.: Adaptation, Selection, and Plasticity in Ongoing Human Evolution.

e. Lasker, G. W.: Migration, Isolation, and Ongoing Human Evolution.

f. Reynolds, E. L.: Radiation and Human Evolution.

665. Roberts, D. F., and Harrison, G. A., editors: Natural Selection in Human Populations, New York, 1959, Pergamon Press, Ltd.

The volume reports a symposium sponsored by the Wenner-Gren Foundation for Anthropological Research and comprising papers read at a 1958 meeting of the Society for the Study of Human Biology. The papers are as follows:

a. Penrose, L. S.: Natural Selection in Man: Some Basic Problems.
b. Owen, A. R. G.: Mathematical Models for Selection.
c. Clarke, C. A.: The Relative Fitness of Human Mutant Genes.
d. Sheppard, P. M.: Natural Selection and Some Polymorphic Characters in Man.
e. Dobzhansky, T.: On Selection of Gene Systems in Natural Populations.
f. Ashton, E. H.: Rate of Change in Primate Evolution.

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666. Hayes, W., and Clowes, R. C.: Microbial Genetics, Tenth Symposium of the Society for General Microbiology, held at the Royal Institution, London, April, 1960, London, 1960, Cambridge University Press.

This collection of thirteen papers sets a high standard of excellence.

667. Cold Spring Harbor Symposia on Quantitative Biology. Vol. XXIV. Genetics and 20th Century Darwinism, Cold Spring Harbor, N. Y., 1959, Biological Laboratory.

Among the papers were the following:

a. Mourant, A. E.: Human Blood Groups and Natural Selection.
b. Barnicot, N. A.: Darwin's View on the Evolution of Human Races in the Light of Modern Research.
c. Sheppard, P. M.: The Evolution of Mimicry; a Problem in Ecology and Genetics.
d. Coon, C. S.: Race and Ecology in Man.
e. Heberer, G.: The Descent of Man and the Present Fossil Record.
f. Hunt, E. E., Jr.: The Continuing Evolution of Modern Man.
g. Rensch, B.: Trends Towards Progress of Brains and Sense Organs.

See Wright for a review and discussion of the symposium. A somewhat comparable collection of papers, designed, however, for lay consumption, appeared in the September, 1960, issue of *Scientific American.*

668. Miscellaneous. "A Bibliography of Human Genetics," assembled by Dr. Richard H. Post, was published in the first volumes of the *American Journal of Human Genetics.* The bibliography was discontinued with the issue of September, 1959. Post provided a subject index for the first eight volumes, published in connection with the December, 1960, issue of the journal. The bibliographies in volumes 9 and 10 are indexed in connection with the rest of the volume.

We suggest that the literature on human genetics is now indexed with reasonable completeness in the following places: literature up to 1946, R. R. Gates' *Human Heredity;* literature from 1948 to 1958, *American Journal of Human Genetics;* literature from 1958 to an indefinite point in the future, JOURNAL OF CHRONIC DISEASES.

II. HISTORY

669. Historical comments were made in many publications, e.g., see ¶872.

Penrose, Ellis, and Delhanty pointed out that in his well-known monograph on the genetic disorders of the eye (1932), Waardenburg suggested a chromosomal aberration as the cause of Mongolism, with nondisjunction mentioned as a possibility.

The John Innes Horticultural Institution of suburban London, of which the first director, Bateson, chose genetics and cytology for its areas of investigation, celebrated its fiftieth anniversary and announced a change in its name to simply The John Innes Institute and the establishment of a cell biology laboratory (Anon.).

670. Stern pointed out that Oscar Vogt, who died on July 31, 1959, at the age of 89, coined the terms penetrance and expressivity in 1926. Vogt was primarily a neuroanatomist and founder of the Kaiser Wilhelm Institut für Hirnforschung in Berlin-Buch. He included in his institute a division of genetics and called to it Timoféeff-Ressovsky, who had been trained in the U.S.S.R. and had first begun his scientific work there.

Vogel gave a short biographic sketch of Hans Nachtsheim on the occasion of Nachtsheim's seventieth birthday.

671. McKusick provided a biographic sketch of Walter Stanborough Sutton (1877-1916), who first formally elaborated and assembled support for the chromosomal theory of Mendelism. A graduate student with E. B. Wilson at the time of his monumental work, Sutton subsequently went into medicine and became a prominent surgeon. Ironically, his premature death was the result of a ruptured appendiceal abscess. The contributions of Boveri to the theory were discussed by Stern in 1950 (Nature, London, Sept. 9).

Darlington presented a review of more recent evidence on the chromosome theory of heredity.

672. Bearn participated in a series of Lowell Lectures planning of which was based on the proposition that some kinds of fundamental advance in science can be made only from study of disease. Beecher, the editor of the published lectures, pointed out that "the university hospitals of the land have long been recognized as fields where already discovered concepts are applied, but now it is evident they are the only places where certain discoveries basic to the advancement of pure science are likely to occur."

Bearn's lecture, "The Contribution of Clinical Medicine to Biochemical Genetics," contains much of historical interest: As Zirkle pointed out, human heredity is alluded to by Euripides in the tragedy *Electra*. In 1646, Sir Thomas Browne in an essay on the "Blackness of Negroes" made first use of the word "mutation" and suggested that this, rather than tanning by the tropical sun, is the cause of dark skin. Bearn quoted, as did Garrod 30 years previously, the letter which William Harvey wrote a few weeks before his death and in which he said, "For it has been found in almost all things, that what they contain of

useful or of applicable nature, is hardly perceived until we are deprived of them, or they become deranged in some way." The concept of constitutional susceptibility to a particular disease, as it developed in the nineteenth century, was mentioned in the lecture. However, "in 1878, the growing belief that hereditary influences were important in the causation of disease received a blow from which it is only now recovering, and which put back the science of genetics fifty years." Bearn referred to Pasteur's germ theory.

Other points of historical interest included Bateson's introduction of the term "genetics" (1905), Garrod's work on inborn errors of metabolism, and the description (1911) of hepatolenticular degeneration by the 33-year-old Kinnier Wilson. Wilson concluded that "although the disease is familial it is not hereditary." Bearn pointed out that "had Wilson appreciated the inherited nature of the disease he might have avoided the heart-breaking task of looking for hypothetical intestinal toxins."

In commenting on Bearn's lecture, his colleague René J. Dubos said in a later lecture, "I would be surprised if the medical geneticist of the future did not rate the sociological aspects of his science more important than its contribution to biochemistry."

III. GENERAL GENETICS, SELECTED REPORTS

673. Terminology. Penrose displayed the acquired trait of editors when he took *Lancet* to task for the use of "monozygous" and "dizygous" instead of "monozygotic" and "dizygotic" for the description of twins and "sibling" rather than "sib" for brother or sister. Carter defended the use of "monozygous" on the basis of euphony and the interchangeable use of "sib" and "sibling," while admitting that the shorter form is a timesaver.

Singleton urged that "epistasis" and "hypostasis" be reserved for use within the limits of the original definition, i.e., to indicate dominant and recessive relationships for genes not at the same locus. He indicates that for alleles, and even for multiple allelic series, the terms dominant and recessive "serve admirably well."

674. Microbial genetics. In a Harvey Lecture, Jacob discussed some aspects of viral genetics.

Austrian discussed the genetics of *Diplococcus pneumoniae* in relation to the elucidation of biologic phenomena.

Yanofsky reviewed the tryptophane synthetase system of *E. coli* and Neurospora. The system is a useful model since multiple allelism, "leaky mutants," suppressors and modifiers, and other phenomena are nicely illustrated.

Levinthal has developed a system in which it should be possible to do fine structure genetic analysis of mutations affecting a single enzyme and at the same time to identify chemical alterations in the enzyme molecule resulting from the mutations. The enzyme alkaline phosphatase produced by the bacterium *E. coli* strain K_{12} has been studied. Technical advantages of the system include the following: (1) the requirements for fine structure mapping are satisfied, (2) methods

for obtaining maximal production of alkaline phosphatase are known, and (3) alkaline phosphatase is a relatively stable and easily assayable enzyme. Garen and Levinthal described a method for purifying alkaline phosphatase from *E. coli* and several of the physicochemical properties of purified enzyme. Grown under conditions of phosphate deprivation, the cells produce alkaline phosphatase to the extent of approximately 6 per cent of total protein synthesized.

Ottolenghi and Hotchkiss found that DNA with genetic transforming activity was released by growing populations of *D. pneumoniae*. "Since mixed cultures thus give rise to recombinants, it may be that transformation provides a natural mechanism of genetic recombination for pneumococcus." Transformation may not be a phenomenon restricted to laboratory conditions.

675. Chemistry of the gene. Using viruses with single chain RNA, Tsugita and Fraenkel-Conrat did experiments bearing on the nature of the genetic code. A general review was given by Sinsheimer.

In a useful review lecture, Taylor discussed chromosome replication and the coding and transmission of the genetic heritage. Penrose expounded a theory of DNA replication. In his Nobel lecture, Kornberg discussed the biologic synthesis of DNA.

Brachet gave a detailed review of the role of ribonucleic acids in protein synthesis. In conclusion he stated, ". . . The common 'slogan': DNA makes RNA, and RNA makes protein, is, in my opinion, an over-simplification, which may prove dangerous." In his introduction he states, "It is hard to believe nowadays how confused the whole field of nucleic acid biochemistry and localization was some thirty years ago . . . . Regarding the role of deoxyribonucleic acid, all one could suggest was that it might play the part of an intranuclear pH buffer."

676. Gene action. The largest protein for which a complete amino acid sequence has been determined is the tobacco mosaic virus with 158 amino acids (Tsugita and colleagues). Tsugita and Fraenkel-Conrat determined the change in a chemically induced mutant of tobacco mosaic virus.

Markert pointed out that the function of the gene is at the focus of both embryology and genetics. The explanation for cell-specific gene function and of time-specific gene function is a matter of central importance in embryology. He pointed out that at least three types of evidence suggest that the chromosomes undergo differentiation with gene activation or inhibition during development: (1) chemical analysis of nuclei and chromosomes from different types of differentiated cells reveals differences not in DNA and in histone but in RNA and residual protein, (2) morphologic changes in chromosomes specific for tissue and for stage of development are demonstrable in some forms, and (3) nuclear transplantation provides evidence of nuclear, presumably chromosomal, differentiation.

Sonneborn reviewed the question of the gene in cell differentiation. He pointed out that nuclei are not functionally equivalent in all cells of the body. There is chemical and morphologic evidence for chromosomal differentiation.

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He pointed out that there is "a marvelous system of give and take among certain genes and between the genes and the cytoplasm. . . . More goes on in the chromosome than mere exact reproduction and uniform action of an invariant set of genes. . . . Small but promising beginnings of an understanding of the mechanisms of gene action in cellular differentiation are already at hand on the molecular level of analysis."

677. Mutation. Scheinberg and Reckel found that the frequency of inagglutinable erythrocytes was increased in pigeons after total body irradiation and in human polycythemic patients treated with P^{32}. Persistence of the increased levels of inagglutinable cells was observed in pigeons for more than 200 days after irradiation and in a polycythemic patient for as long as 173 days after treatment. The authors concluded that mutation was the origin of the inagglutinable cells.

Heiner and colleagues found in barley diverse ratios of mutations to chromosome aberrations depending on whether diethyl sulfate or gamma rays were used. The fundamental significance is that it suggests the mechanism of action is different in the two cases. The practical significance is that it suggests the possibility that breeders can induce many mutations, at low cost, with minimal disruption of the chromosome complement.

Rudner presented evidence that mutation is an error in base pairing.

Brink discussed *paramutation.* One of the basic principles of Mendelian theory is that in replication of the genetic material each element determines the formation of a precisely equivalent element. It is understood that different germinal elements do not react with each other in the replication process and that the nature of the product is not affected by the environment. Mutation is the only established exception to this law, but only so far as the actual event is concerned; the mutant form behaves thereafter according to the rule.

Brink's thesis assumes "that the genonema is of a dual nature, incident upon its heterocatalytic function, and that mutation and paramutation reflect alterations in the two respective kinds of components." Paramutation displays the following characteristics: (1) the new form arises in response to some action associated with an allele in the homologous chromosome, (2) the genetic change occurs in 100 per cent of the cases, (3) the process seemingly is nonreciprocal, (4) the response is specific in each case, (5) partial reversion to the wild type is characteristic of all paramutants thus far observed, and (6) the paramutant form also becomes paramutagenic, although weakly so.

678. Twinning. Erb and his colleagues demonstrated the inheritance of twinning in Holstein-Friesian cattle. The precise mode of inheritance could not be determined. It was estimated that monozygotic twinning represented about 7.4 per cent of all twin births. Realization of precise genetic ratios would, they felt, be frustrated by such factors as fertilization of only one egg from a double ovulation, death of one embryo and not of the other, inability of some uteri to accommodate a twin pregnancy (possibly also inherited), and others. Twinning rates increased with the age of the cow and the number of calvings. A high abor-

tion rate observed in twin pregnancies suggested that mortality of one or both embryos may be greater at earlier stages as well.

Stone and colleagues studied the blood groups of progeny from two dizygotic twin bulls in which erythrocyte mosaicism was present. The progeny in each case showed blood groups which were interpreted as indicative that the exchange of hematopoietic tissue in early embryonic life had had no influence on the germ plasm of the alternate bulls. Thus, evidence against Galton's pangenesis theory and against recent revivals of it is provided.

Miscellaneous: 679. Kerr described a strain of DDT-resistant housefly in which all males are resistant and the resistance is transmitted by males but not by females. "It is therefore determined directly by a Y-chromosome factor or, like sex in *Drosophila*, by the balance between the unpaired parts of X and Y and the rest of the chromosome set." Craig, Hickey, and VandeHey described an inherited male-producing factor in *Aedes aegypti.* Not only did the factor result in production of predominantly males, but it appeared to be transmitted only by the male.

In the rabbit, Weil found that spermatozoa from the epididymis lack the antigenic material present on seminal spermatozoa. The observation supported the view that antigenic material is taken up by the spermatozoa from the seminal plasma.

In rabbits, Emmens could demonstrate no effect on sex ratio by artificially changing the pH of the vagina.

An inherited abnormality of sex ratio was discussed in Drosophila by Malagolowkin, Carvalho, and da Paz and in mice by Weir.

Exobiology, the study of life beyond the earth, obviously has important genetic implications (Lederberg).

680. Nossal described further work supporting the view that no cell will produce more than one type of antibody at one time (¶343). He isolated, in microdroplets, single lymph node cells from rats immunized against more than one bacterial antigen. He selected those which appeared to be plasma cells; the success of selection was checked by staining some of them. Production of antibody by these cells was detected and measured by the introduction of successive batches of motile bacteria into the droplets until no further immobilization occurred. Antibodies were thus demonstrated against all the antigens received by the animal, but no cell produced more than one antibody. These results are consistent with the clonal selection theory of acquired immunity.

A Beltsville Small White turkey of parthenogenetic origin hatched, matured, and produced semen containing viable sperm. Semen from this male was used to inseminate fourteen turkey hens. Three hundred twenty eggs were incubated; 122 poults, about equally divided as to sex, hatched unaided from 145 fertile eggs (Olsen). Olsen also gave a summary of 9 years' experience with parthenogenesis in turkeys.

The Committee on Standardized Genetic Nomenclature for Mice gave a second listing.

IV. HUMAN AND MEDICAL GENETICS, GENERAL CONSIDERATIONS

681. Reviews. A general discussion was provided by Kretchmer, among others.

A moderately long review of medical genetics was provided by Hsia.

Polymorphic Systems in Man.—

682. Haptoglobins (Fig. 28). Matsunaga and Murai estimated the frequency of the Hp^1 gene to be 0.238 (with a standard error of 0.016) in Japanese—a figure lower than in Caucasians and Negroes but slightly higher than in Asiatic Indians. Haptoglobin gene frequencies in Germany and Austria were reported by Baitsch and colleagues. Allison and Barnicot reported on haptoglobins and transferrins in some eastern African peoples, and Sutton and colleagues studied them in Mexican and Guatemalan Indians. Moullec, Fine, and Linhard studied the distribution of haptoglobin types in Dakar, Senegal.

Giblett and Steinberg presented evidence for a third haptoglobin allele, $Hp^{2\,m}$, which is responsible for the 2-1 modified phenotype and probably also for ahaptoglobinemia (not caused by excessive red cell destruction) when in combination with Hp^1. The conclusions were based on a study of ninety-two Negro families. The Hp^{2m} allele appeared to have a frequency of about 0.145 in the American Negro.

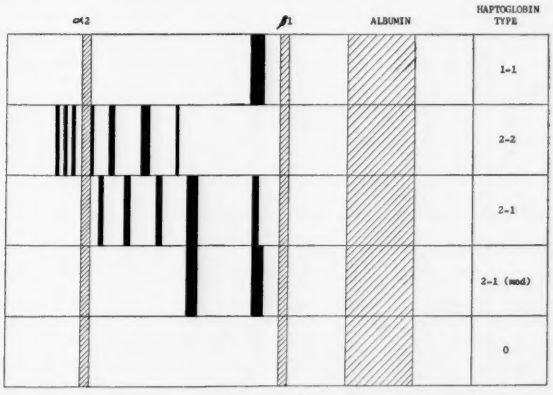

Fig. 28.—Haptoglobin types. Diagrammatic representation, as demonstrated on starch gel electrophoresis. The solid black is haptoglobin, the diagonals other protein. (From Giblett, E. R., and Steinberg, A. G.: Am. J. Human Genet. 12:160, 1960; published by the American Society of Human Genetics.)

Harris and colleagues described an interesting family in which two rare serum protein phenotypes were segregating: A modified 2-1 haptoglobin phenotype and an unusual transferrin referred to by these workers as B_2.

Blumberg found no polymorphism of haptoglobins in primates other than man. (Polymorphism of transferrins was found in monkeys.) However, Beckman and Cedermark studied haptoglobin types in ten *Macaca irus* monkeys and found seven Hp 1-1 and three Hp 2-1. The 1-1 type seemed identical to those similarly identified in man. "It is known also that African Negroes have a high frequency

of the Hp-1 gene. Hence this gene might have a selective advantage in tropical areas." In seventeen specimens from *Macaca rhesus*, ten from *Macaca radiata*, and four from three other primate species, Mäkelä, Renkonen, and Salonen found only a haptoglobin pattern resembling Hp 1-1 of man. In twenty-five cynomolgous monkeys (*M. irus*), Boyer and Young in this laboratory observed only the 1-1 type. Also, only 1-1 was found in two spider monkeys (*Ateles geoffroyi?*), one green monkey (*Cercopithecus aethiops*), one red monkey (*Erythrocebus patas*), twenty-five chimpanzees (*Pan troglodytes*), and two gibbons (*Hylobates lars*). Haptoglobin types in monkeys were studied also by Arends and Rodriguez.

Javid and Horowitz described an improved technique for quantification of serum haptoglobins. Hirschfeld suggested that agar gel electrophoresis may be a valuable supplement to starch gel electrophoresis in cases of doubtful haptoglobin findings by the latter technique. "In some instances repeated starch-gel electrophoretic investigations of certain sera did not demonstrate any haptoglobin in these sera, although in agar-gel electrophoresis haptoglobins were demonstrable, enabling us to group these sera." By immunoelectrophoresis, he differentiated haptoglobins from another group-specific and heritable serum protein system he has discovered (¶690).

Tombs demonstrated some binding of hemoglobin by a β globulin. Much less hemoglobin was bound by this protein than by haptoglobin, an α_2 globulin. In rabbits, Murray and Connell noted elevation of serum haptoglobin when turpentine abscesses were produced.

683. Transferrins. Gahne, Rendel, and Venge reported on the inheritance of β globulins in serum and milk of cattle. Boyer and Young described polymorphism of the β globulins (transferrin) in twenty-five chimpanzees among which they found seven β globulin phenotypes. Lai and Kirk studied β globulin variants in two species of monkey, *Macaca mulatta* and *M. irus*.

By starch gel electrophoresis, Shreffler studied the transferrins in thirteen inbred lines of mice. One of these, the DBA line, differed from the others in the substitution of a more rapidly migrating component for the one present in the other lines. The f_1 progeny from reciprocal outcrosses of DBA contained both components in about equal amount, but each was reduced in quantity relative to the parent lines. Tests of 501 f_2 and backcross progeny showed segregation compatible with the existence of codominant alleles. Tests for linkage with the agouti and the hemoglobin loci were negative.

In man, Harris and his colleagues described a new transferrin type they call D_4. Two families were studied. It behaves as a codominant. The phenotype frequency was about one in 500 in English and Italian persons. It was not found in 250 Africans.

684. γ Globulins. Steinberg, Giles, and Stauffer reported on a new Gm type ("Gm-like") which was present in 27.5 per cent of 403 Negroes and in none of 250 white persons. It was inherited as a dominant trait. (It perhaps will be called Gm^e in due course.) They presented evidence suggesting that Gm specificity is a function of the total RA serum–anti-D serum reacting system and not of one

component alone. The distribution of Gm^a and Gm-like alleles in several populations was studied (Steinberg, Stauffer, and Fudenberg).

Steinberg, Stauffer, and Boyer described another new Gm allele in the American Negro, Gm^{ab}. This is a sixth allele, the previously described ones being Gm^a, Gm^b, Gm^x, Gm^{ax}, and Gm-like (see ¶354). Assuming that the Negro ancestors of the American Negro were homozygous for Gm^{ab} and that the alleles Gm^a and Gm^b were derived from white ancestors, the sum of the frequencies for the latter two alleles (0.31) is a measure of the proportion of the American Negro genotype derived from white ancestors. This estimate is in close agreement with that of Glass and Li (1953) who, on the basis of Rh blood groups, placed the proportion at about 30 per cent.

Ropartz and colleagues found yet another Gm group they call InV. It was found in both white persons and Negroes.

Lawler found the frequency of the Gm (a+) phenotype to be 60.98 per cent in Great Britain and 40.18 per cent in the Ferrara district of Italy. Family studies in both populations—relative proportions of three mating types, the occurrence of all Gm (a−) children from two Gm (a−) parents, relative proportion of families all Gm (a+) or some Gm (a−) from parents at least one of whom is Gm (a+)—supported the hypothesis that the Gm (a+) phenotype is determined by a gene which is expressed in the heterozygote. Milk from Gm (a+) mothers showed no inhibition. In milk, γ globulin is low.

Harboe studied the relation of Gm type to rheumatoid arthritis forms of hemagglutinating substances in eighty-two specimens of serum with a strongly positive result in the Waaler-Rose test.

Steinberg and Stauffer demonstrated differences in heat stability of the several Gm types. Furthermore, they reported the puzzling finding that Gm (a−) and Gm (x−) were changed to Gm (a+) and Gm (x+) by heating.

In man, using chicken antisera to human γ globulin, Goodman has demonstrated variations the genetics of which should be investigated. He also studied sera from nonhuman primates and commented on the desirability of studying the relations of these γ globulin variations to Gm types.

Dray and Young have studied the genetics of isoantigenic γ globulins in rabbits. They conclude that the isoantigenic sites (called by them RGG-I and RGG-II) are controlled by a single allelic pair of autosomal genes with both specificities exhibited by the heterozygotes. The three genotypes are designated by them as follows: γ^I/γ^I, γ^{II}/γ^{II}, and γ^I/γ^{II}.

685. Isoniazid metabolism. In studying isoniazid metabolism in man, Evans, Manley, and McKusick used as a test dose 10 mg. orally per kilogram of body weight. The level of free INH in the plasma 6 hours after administration proved a satisfactory basis of classification of the subject as either a rapid inactivator (i.e., rapid acetylator) or a slow inactivator. On the basis of a study of fifty-three families, it was concluded that a single pair of genes is responsible for the polymorphism and that slow inactivation is an autosomal recessive trait. In both Caucasian and American Negro populations, about 50 per cent are slow inactivators.

Using an intravenous fall-off technique and a chemical method of determination, Jenne found that most subjects fell into two groups with respect to the metabolism of isoniazid: those with a mean half-life of 59 minutes and those with a mean half-life of 159 minutes.

Armstrong and Peart found that 95 per cent of Eskimos are rapid inactivators of INH and that in the 5 per cent slow inactivators there was suspicion of white admixture. By their method (microbiologic determination of free INH of blood 6 hours after administration of 4 mg. per kilogram body weight), 44 per cent of non-Eskimos were rapid inactivators.

Peters described a fluorometric method for measuring isoniazid in plasma.

686. PTC tasting. Pons contributed to the genetic knowledge of PTC tasting. Sibship data supported the hypothesis that nontasting is recessive.

In Brazil, Freire-Maia and Quelce-Salgado found frequencies of nontasters of 38, 26, and 8 per cent in three different populations. Variations within single individuals in PTC taste sensitivity were shown. No significant difference in PTC taste sensitivity between smokers and nonsmokers was found. Freire-Maia also analyzed a large amount of data obtained by different workers in different populations and again could find no evidence of any interaction between tobacco smoking and taste sensitivity to PTC.

Fischer and Griffin provided a progress report on work directed toward elucidation of the enzymatic basis of PTC tasting and nontasting. Skude investigated the variation of PTC tasting which consists of a sweet taste.

Miscellaneous Genetic Polymorphisms.—

687. Gerber, Gerber, and Altman described a new method of quantitative determination of *urinary β aminoisobutyric acid.*

688. In a monograph on leukocyte antigens and antibodies, Walford described techniques and reviewed critically the information which is available bearing on the probably genetic polymorphism of *leukocyte antigenicity.*

689. Stern (p. 232 of his textbook, ¶657) refers to studies of the *inability to smell hydrogen cyanide.* In an Australian study (Nature, London, 1953) and a Japanese study (Jap. J. Human Genet., 1957), the trait appeared to be sex-linked recessive. Gwilt wrote further on the matter but did not contribute to understanding of the genetics of the trait.

In a group of Russian immigrants to Brazil, the Freire-Maias with Quelce-Salgado found that 91 per cent had the R type of arm folding (right arm uppermost), whereas the frequency was about 40 per cent in most previously studied populations.

In Japan, Kusaji studied the population genetics of absence of the palmaris longus muscle. The frequency was 3.69 per cent. The frequencies in parents and siblings of probands were, respectively, 6.3 and 7.6 times that in the general population. The author suggested autosomal dominant inheritance with reduced

penetrance. He calculated a probability of 0.853 that the anomaly would appear in at least one hand of a heterozygote. The frequency of the gene was estimated to be between 0.0234 and 0.0377. There was no increased parental consanguinity or birth order, and maternal age had no effect.

690. By two dimensional electrophoresis (filter paper followed by starch gel), Poulik, Zuelzer, and Meyer demonstrated within the zone moving rapidly on paper two proteins, other than albumin, which they called "*albumin-like*" and "*quasialbumin.*" Various individuals showed both, one, or neither of these. Their genetics should be studied.

By immunoelectrophoresis, Hirschfeld and Beckman demonstrated a new genetically determined *group-specific serum system*, Gc. They suggest that the genes be termed Gc^1 and Gc^2 and the genotypes corresponding to the three phenotypes "fast," "two-peaked," and "slow" be designated Gc 1-1, Gc 2-1, and Gc 2-2, respectively. They could demonstrate no relationship to the haptoglobin, Gm, or transferrin systems or association with cholinesterase type. There was also no demonstrable relationship to the blood group antigens with the exception of the P system.

Hirschfeld, Jonsson, and Rasmuson studied the inheritance of the new group-specific human serum protein system demonstrated by Hirschfeld using an immunoelectrophoretic technique. There are three phenotypes: a fast-moving precipitating component (group 1), a slow-moving precipitating component (group 3), and a precipitating component giving two peaks (group 2). The protein involved migrates in the α_2 region near the haptoglobins but is not haptoglobin, since it does not bind hemoglobin and since there is no correlation between the Hirschfeld and haptoglobin types. Family studies demonstrate inheritance as a codominant trait. None of 76 type 1 mothers had a type 3 child. None of 14 type 3 mothers had a type 1 child. The allele responsible for the fast-moving component was found to have a frequency of 0.74, the other allele a frequency of 0.26.

In monkeys, Dray prepared precipitating antibodies specific for three normal α globulins of man. The antibodies were demonstrated by immunoelectrophoresis. The demonstration of possible genetic differences by this approach was mentioned as one use.

Battisto demonstrated a delayed skin reaction in guinea pigs injected for the first time with serum from a different guinea pig. Evidence was presented for the existence of genetically variable serum protein types, on the basis of potential for inciting delayed isohypersensitivity in other individuals of the same species. "The grouping of guinea pigs on the basis of the presence or absence of heritable serum factor appears fundamentally similar to the differentiations made within other species based on the occurrence of heritable substances in the sera of some but not all individuals." The serum antigen in the guinea pig seemed to Battisto most analogous to the Lewis antigen of man and the J substance of cattle. "The existence in the guinea pig of what is evidently a new type of iso-immune state, namely delayed iso-hypersensitivity, suggests the possibility that a similar state may occur in other species."

Morell and Scheinberg, by separation on DEAE cellulose columns and subsequent starch gel electrophoresis, demonstrated apparent genetic polymorphism in human *ceruloplasmin*. Family studies would be of interest.

691. Kaplan and colleagues demonstrated molecular heterogeneity of the lactic dehydrogenases from different tissues and from different animals by differences in the effects of coenzyme analogues. They pointed out that enzyme heterogeneity has been demonstrated by immunologic techniques and by differences in physical properties such as molecular weight and electrophoretic mobility and that determination of amino acid sequence is an elegant approach to the study of such heterogeneity. They had found previously that isonicotinic acid hydrazide (isoniazid) strongly inhibits some diphosphopyridine nucleotidases and not others. Their recent work has shown molecular heterogeneity in lactic dehydrogenases by differences in enzymatic activity when different pyridine-substituted analogues of diphosphopyridine nucleotide were used.

Schwartz studied the genetically variant esterases of maize. Three allelic genes, E^F, E^N, and E^S, were identified. Heterozygotes were shown to have a hybrid enzyme in addition to the two parental types.

692. Multiple births. Bulmer found that mothers, but not fathers, of twins are more often twins than expected. There also appeared to be an increased twinning rate among the children of the sisters of the mothers of twins. Weinberg early in this century concluded that dizygotic, but not monozygotic, twinning is hereditary and that the heredity involved is limited to the mother's side. (See Fig. 29.)

Bulmer found the monozygotic twinning rate to be rather constant among Europeans and Negroes—about 3 to 4 per 1,000 births. Dizygotic twinning showed considerable variation in rate, being higher among Negroes. Considerable variations in different parts of Europe were demonstrated. The lower half of the Italian "boot" has a high dizygotic rate. Much of Spain and southwestern France have an unusually low rate.

By an extension of Weinberg's differential method of estimating the proportions of identical and fraternal twins and on the basis of some plausible assumptions, Allen estimated the expected number of zygotes responsible for triplets and higher plural births. On the basis of United States statistics, he estimated that the ratios of one egg to two egg to three egg triplets are 1:3:2 for Negroes and 1:2:1 for Caucasians. The four ovularity types of white quadruplets were estimated to have the relative proportions of 2:6:5:4.

Valaes and Doxiadis described two pairs of monozygotic twins; in each case one twin had anemia (hemoglobin 8 and 13 Gm.) and the other had polycythemia (28 and 23 Gm.). The polycythemic infant was larger in each case. A potential bias of twin studies is the exaggeration of differences in the antenatal environment of monozygotic twins as compared to dizygotic twins because of vascular competition. The method of contrasting concordance rate in monozygotic twins and in dizygotic twins of like sex assumes identical antenatal and postnatal environment of twin pairs in both categories. It seems clear that antenatal differences

in environment are greater in monozygotic twins; postnatal differences in environment are greater in dizygotic twins.

Jarvik and colleagues found greater differences in age of death of two egg twins than of one egg twins. The differences by zygosity were greater in female pairs than in male pairs. The proportion of one egg twins was 30.6 per cent. Methods used in zygosity diagnosis were not indicated in the report. The same group (Falek and colleagues) showed that the greater biologic similarity of monozygotic twins extended into old age. Specifically, in a group of twins over 60 years of age, the life span was less different in monozygotic than in dizygotic twins, as were also the results of psychometric tests. Again, the method of zygosity diagnosis raises questions about the interpretation of these results.

Renal transplantation between identical twins (Dossetor and associates) and, by special methods to incapacitate the immune mechanism, between fraternal twins (Merrill and associates) was discussed.

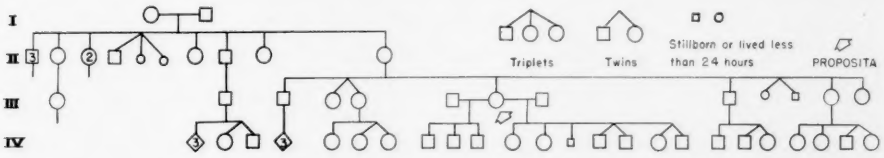

Fig. 29.—Pedigree of a remarkable family in which an unusual number of multiple births have occurred, especially in the female lines. Note that the woman in generation I had triplets among her offspring, two sets of twins among her grandchildren, and six sets of twins among her great-grandchildren.

Population genetics: 693. Goldschmidt, Ronen, and Ronen found a first cousin marriage rate of 1 to 2 per cent in Ashkenazic Jews in Israel. The parents of babies born from 1955 to 1957 were studied. Other Jewish groups showed far higher rates of consanguinity. The authors doubted that the frequency reflected the sizes of the isolates in the Diaspora. The nonrandomness of the consanguinity was indicated by the preference for marriages between children of siblings of the same sex. The mean number of live children after different durations of marriage was less in cousin families than in others.

Ishikuni and colleagues described the Japanese island Hosojima, which has one of the highest rates of inbreeding recognized anywhere in the world. A coefficient of inbreeding of 0.3341 was estimated. Two hereditary diseases, deafmutism and dyschromatosis symmetrica hereditaria, were described in the population. In the latter condition, the disease is of cosmetic effect only. The inheritance of both states is probably recessive, but pseudodominant (or quasidominant, see ¶730) heredity results from the high degree of inbreeding.

Shaw pointed out that the use of the surname of both the mother and the father makes it easy in Spanish-speaking countries to suspect consanguinity. "In every marriage of first cousins the spouses will have one surname alike."

694. Darwin gave a pessimistic view on the political practicability of efforts by man to control his numbers. At the same time he recognized the importance of such measures.

Foerster, Mora, and Amiot estimate that if the human population grows as it has grown in the last two millennia, its numbers will approach infinity on Friday, Nov. 13, A.D. 2026. This precise calculation is actually accurate, in the claim of the authors, to within 10 years. Obviously it is for emphasis and effect that they time it so exactly and particularly choose a Friday the thirteenth!

Doyle, Ewers, and Sapit described the development and use of a fertility testing tape based on the content of glucose in the mucus from the cervix. The paper tape is impregnated with glucose oxidase, which catalyzes the oxidation of glucose to gluconic acid. Hydrogen peroxide, a by-product of the reaction, with a peroxidase, changes the color of the oxidizable dye in the tape from pink to blue. Tests in women undergoing laparotomy revealed the appearance of glucose in cervical mucus to be related to escape of the ovum from the Graafian follicle.

Miscellaneous: 695. Considerations bearing on the *sex ratio in man* were discussed by Bodmer and Edwards, by Edwards and Fraccaro, by Comfort, and by others.

Tricomi, Serr, and Solish did sex chromatin determinations in the aborted material in 242 cases: 149 were "male" and 93 were "female." A preponderance of males was found at every stage back to 4 weeks. The primary sex ratio must be much higher than the secondary sex ratio of about 106:100 at birth. Furthermore, the male preponderance in the secondary sex ratio is not due to preferential loss of females in the fetal period.

Discussion of why a sex ratio of about one-half is selectively advantageous was engaged in by Kalmus and Smith, by Bodmer and Edwards, and by Edwards. Kalmus and Smith believe that there are two main selective forces: one which requires maximum probability for the encounter of a male and a female at the reproductive age, the other that the genetic variance of a population should be as great as possible. Bodmer and Edwards support a Fisherian hypothesis: that the most important selective force arises through the advantage of reproducing as efficiently as possible, that is, of making the maximum genetic contribution to future generations at the lowest cost in terms of effort spent in bearing of young (Fisher: *The Genetical Theory of Natural Selection*).

Szilard presented data on decrease (from 1.067 to 1.036) of the sex ratio with advancing age of the father and suggested that they lend support to his theory of aging: that the accumulation of random "hits" suffered by the chromosomes is the basic mechanism of natural aging. He suggested that a hit of the X chromosome of the spermatogonium might result in failure of that cell to develop further; a hit of the Y chromosome might permit further differentiation but only into X-bearing sperm. (See ¶347.)

Comfort suggested that horse-breeding records might provide an answer, since there is in this species little or no correlation between ages of parents and stallions are used for breeding purposes to a rather advanced age.

696. Djordjevic and Szybalski found that a human cell line could be cultivated indefinitely in the presence of up to 3×10^{-5}M 5-bromodeoxyuridine (BUDR) without loss of viability. BUDR replaces up to 45 per cent of the thymi-

dine of DNA and renders the cells highly sensitive to ultraviolet light and x-ray. The potential usefulness of this method of radiosensitization in the radiotherapy of neoplastic disease was discussed.

697. In the rhesus monkey, Bangham, Hobbs, and Tee showed that radiolabeled proteins passed from the fetus into the mother's circulation.

698. Shettles studied dried, unstained smears of human spermatazoa by phase contrast microscopy and demonstrated two distinct populations regarding head and nuclear size, shape, and diffraction of light (Fig. 30). He concluded that the smaller heads contain the Y chromosome and the larger the X chromosome. Ramifications of this study to investigate interindividual and intraindividual variations in head size, the proportions of the two types, differential migration rate in capillary tubes, and the use of the morphologic method as a check on the

Fig. 30.—Dimorphism of human sperm? Dried, unstained smear of human spermatozoa in phase contrast (×1,000; reduced 1/5). (From Shettles, L. B.: Nature, London 186:648, 1960; published by Macmillan & Co., Ltd.)

efficacy of methods of separation will be awaited with interest. Shettles published a photograph which he interpreted as demonstrating not only the chromosomes but also a difference in the arrangement of the chromosomes in sperm of the two types. His report evoked strong expressions of skepticism from Rothschild at Cambridge University and from Bishop of the Department of Embryology, Carnegie Institute. Rothschild reviewed all the methods which have been tried for separating X and Y spermatozoa—pH, immunologic means, electrophoresis, size and shape of the head—and concluded that "there is so far nc evidence that physical differences have been found between X and Y spermatozoa." Bishop pointed to "the compounded artefacts of air-dried shrinkage and phase-contrast optical aberration."

Van Duijn stated, "In my opinion there cannot be the slightest doubt that Shettles has misinterpreted a number of optical artefacts." He proceeded to explain on the basis of physical optics the artefacts which can develop in phase microscopy. He also gave cytologic reasons for questioning the observations of Shettles. However, Shettles remains convinced of a demonstrable morphologic dimorphism of sperm.

699. Garn and colleagues found that children selected for study according to the *body build* of their parents differed in rate of growth and in timing of osseous development. Offspring of large-chested parents were taller and heavier and more advanced in skeletal development than were offspring of persons with narrow chests.

700. Gates made reference to twenty pedigrees from India which suggest very strongly that the character hairy ears is indeed holandric (Y linked). Publication of the detailed pedigrees will be awaited with interest.

701. Motulsky discussed metabolic polymorphisms and the role of infectious diseases in human evolution. He considered the evolutionary impact of starvation and of infectious diseases such as tuberculosis, measles, smallpox, and malaria. The relation of malaria to the world distribution of glucose-6-phosphate dehydrogenase deficiency, sickle cell disease, and thalassemia was reviewed. Myxomatosis in the rabbit was used as a model of the evolutionary interrelationships between host and parasite. Since the haptoglobins are increased in a variety of acute and chronic diseases and since transferrin is a potent inhibitor of bacterial and viral multiplication, the polymorphisms in these serum proteins may have originated not because of hemoglobin-binding and iron-binding capacities but because of the selective action of infectious diseases in the past.

702. Muller's suggestion that man should control his evolution by preservation of semen, by artificial insemination, and by parthenogenesis (¶371) brought forth from Nemerov, writer and teacher, of Bennington College, a charmingly written essay pointing out the absurdity and danger of any such measures for the foreseeable future. To Muller's suggestion that man's genetic heritage should be preserved (by sperm banks, for example), Nemerov raised the following objections:

a. "Might not the prospect of a few hundred Offenbachs in the next generation seem to us absurd and not a little sinister. So much more a gaggle of Shakespeares. And what becomes of the idea of the individual?

"Would the genes of Beethoven produce new Beethovens who could compose—to take it with the most naive literalism—the sonatas of Beethoven? But we already have those. Well, then, a little less literally, would they write in the style of Beethoven—imitation Beethoven sonatas? Worse yet (and we already have some of those, too)."

b. "Presumably this endowment inseparably contains *all* and not only some of the traits of the person it produces. Would society then settle for the reproduction of numerous . . . Leonardos in whom painting and pederasty go together?" [Or numerous Beethovens with otosclerosis?]

c. "How do you make up your mind which genetic endowment is the most precious? . . . Imagine the danger to foster parents, not to mention the children, who had opted and received likenesses of Stalin, and then had to cross the periods of Beria, Malenkov, and Khrushchev, with those fatal images growing daily more recognizable beside them."

Addressing himself especially to parthenogenesis, Nemerov raises several objections. "... The idea of 'duplicating' an 'individual' contains a contradiction."

"What is Leonardo to do in the world, given that he is once again Leonardo? . . . The line of thought . . . here approaches the popular Sunday-supplement question, What Would Jesus Do If He Returned to Earth Today? . . . Parthenogenesis . . . might be described as incest squared, or as fertile masturbation, or as sexual solipsism.

"The children of the day after tomorrow, and theirs into remote ages, are to live not merely among the ruined cathedrals and nonsensical superstitions of their progenitors, which is what people do already, but also under a genetic compulsion to repeat indefinitely the shallow virtues, moderate intelligences, and doom-ridden fantasies of the same.

"In passing he [Muller] recommends his remedy as a 'response to the challenge arising from the modern uses of radiation.'

"But with all good will, I cannot see that the scientist, who has made available 'the modern uses of radiation' which he admittedly is unable to control and does not accept responsibility for, can claim in advance that on account of his responsibility and control, the consciously organized breeding of human beings for particular purposes, even if these are thought to be virtuous ones, will not in the same way come into the hands of the possessors of political power."

703. Glass gave a scholarly analysis of the genetics of *aging*, with proposals for further investigations.

V. METHODS

Statistical methods: 704. DeGroot and Li, using the MNS system as an example, described a simplified method for estimating *gene frequencies* from data on phenotype.

Klinker pointed out that a reduced rate of manifestation of a dominant gene can give rise to pedigrees of several types: isolated cases, two or more cases in one generation only, and so on. Using a two generation model and paying proper respect to the method of ascertainment, he calculated the expected frequency of these different types of pedigree patterns for a dominant trait according to the rate of manifestation.

Edwards, in a provocative article entitled "The Simulation of Mendelism," pointed out the difficulties, in the case of relatively common conditions, in distinguishing the effects of major genes and of *polygenic systems*. He stated that discontinuous variation suggesting monofactorial inheritance could result from a polygenic effect if developmental punctuality in the fusion of parts or a biochemical threshold were involved.

In simple cases of multifactorial inheritance with an abrupt threshold so that a proportion p of the population lies beyond the threshold, familial aggregation shows an approximate relation to p which is simple. A trait with the frequency p would be expected to occur in first degree relatives of propositi in a frequency of the order of $\sqrt{p}$.

705. Gittelsohn analyzed the distribution one would expect for qualitative characters in sibships "when sibship size is dependent on the composition as it is sequentially obtained during the course of reproductive history. Such a situation arises in practice when parents limit their families on the basis of producing a child or children with a given defect or after obtaining a desired sex combination among their offspring."

706. Oakland reviewed the statistical analysis of *genetic linkage* data, discussing in particular scoring procedures using "u-statistics." It would seem that this approach is much more complicated and difficult than that of maximum likelihood and the use of an electronic computer.

707. The Freire-Maias presented a formula for calculation of the mean number of lethal and abnormal equivalents per person, using data on abortions, stillbirths, mortality before mean marriage age, and consanguinity.

Frota-Pessoa and Saldanha presented a method by which the spontaneous rate of mutations for recessive sex-linked detrimental characteristics in man may be estimated from the excess of deaths of males over females during uterine life. They suggest and illustrate its use in estimating the doubling dose of radiation in man.

708. Others. Ohkura described the system of family registration which has been in operation for a long time in Japan and discussed the use of the system in the study of human genetics. The "linkage" of vital statistics and health records on a family basis useful for genetic studies has been a concern in western countries in recent years (¶379). The Japanese experience may be useful as a model.

Ebbing discussed the evaluation of medical records for creating a genetic registry.

Simmons and colleagues described experience with zygosity diagnosis of 103 twin pairs, using A_1A_2BO, MNS, Rh, P, Duffy (Fy^a), Kell (K), and Lewis (Le^a).

Eagle reviewed metabolic studies of human cells in culture. He pointed out that the fact that these cultures usually fail to carry out the specific biochemical functions associated with their organ of origin poses serious limitations in their applicability to the study of mammalian physiology. The use of human cell cultures for genetic study was discussed by Chang, by Krooth and Weinberg, and by Sachs and Krim.

VI. CYTOGENETICS IN MAN

709. Reviews and general considerations. Gross edited a second New York Academy of Sciences Conference on the mechanisms of cell division. Twenty-two papers were presented.

The Cell Nucleus, proceedings of a meeting of the Faraday Society held in 1959, was published under the editorship of Mitchell.

The Symposium on Cytology and Cell Culture Genetics of Man held at the 1959 annual meeting of the American Society of Human Genetics was published

in the March, 1960, issue of the *American Journal of Human Genetics*. Selected aspects will be noted here. Chu pointed out that since the structure of metaphase chromosomes has only limited use for the detail required for a cytogenetic map, studies of pachytene chromosome structure should be actively pursued. Ford suggested that in those cases of the Turner syndrome which appear to be XO/XX mosaic, it is possible that the individual develops from an XO zygote but that XX cells arising through nondisjunction are favored and multiply preferentially. The alternative—that some XO cells develop through loss of an X chromosome by nondisjunction—seems less likely. Although nondisjunction in the female could well account for XX ova, in the male the X and Y chromosomes are not associated in a considerable proportion of primary spermatocytes. Random assortment might result in spermatid nuclei which contained both X and Y and in others with neither. Ford stated that no viable trisomic trait in mammals had been demonstrated before Mongolism. As work for the future, he mentioned the possibility of racial polymorphism in the chromosomes and study of the meiotic chromosomes for evidence on nondisjunction, for identification of chromosomal bases for infertility such as reciprocal translocations and both paracentric and pericentric inversions, and for possible discovery of deficiencies in the pachytene chromosomes (in dominantly inherited malformations) which escape attention in somatic chromosomes. Sachs and Krim mentioned 2 patients with the Turner syndrome and with two chromocenters in some cells, none in others; the possibility of XXXX/XO mosaicism to explain the observation was mentioned. The rejection of male to female skin grafts in inbred mice was mentioned as evidence of Y-linked antigenic differences.

General reviews were given by Lenz, by Ford, by Ferguson-Smith, by Ferguson-Smith and Johnston, by Carter, and by Kounow, among others.

In October, 1960, the first issue of the *Human Chromosome Newsletter* appeared. It is assembled and distributed by Dr. David G. Harnden and Miss Patricia A. Jacobs, Western General Hospital, Edinburgh. Its purpose is rapidly "to circulate information on new discoveries and important technical advances in the field of human cytogenetics." The editors emphasize that it is not an official publication and that material contained in it is under no circumstance to be cited without the express permission of the authors.

710. A group of fourteen students of the human chromosomes met in Denver to elaborate a standard system of nomenclature for the human mitotic chromosomes (Robinson). In attendance were Böök and Fraccaro (Uppsala), Chu (Oak Ridge), Ford (Harwell), Harnden and Jacobs (Edinburgh), Hsu (Houston), Hungerford (Philadelphia), Lejeune (Paris), Levan (Lund), Makino (Japan), Puck and Robinson (Denver), and Tjio (Bethesda).

The recommendations were that the autosomes should be numbered serially 1 to 22 in descending order of length, that the sex chromosomes should be indicated X and Y rather than by number, and that the twenty-two autosomal pairs be further divided into seven groups (Table XIII). It was granted that in group 6-12 (the X chromosome resembles members of this group), distinction between chromosomes is difficult.

A footnote contained the following recommendations: "In contemporary publications the terms karyotype and idiogram have often been used indiscriminately. We recommend that the term *karyotype* be applied to a systematized array of the chromosomes of a single cell prepared either by drawing or by photography, with the extension in meaning that the chromosomes of a single cell can typify the chromosomes of the individual or even a species. The term *idiogram* would then be reserved for the diagrammatic representation of a karyotype, which may be based on measurements of the choromosomes in several or many cells."

TABLE XIII. CONSPECTUS OF HUMAN MITOTIC CHROMOSOMES

Group 1-3	Large chromosomes with approximately median centromeres. The three chromosomes are readily distinguished from each other by size and centromere position.
Group 4-5	Large chromosomes with submedian centromeres. The two chromosomes are difficult to distinguish, but chromosome 4 is slightly longer.
Group 6-12	Medium-sized chromosomes with submedian centromeres. The X chromosome resembles the longer chromosomes in this group, especially chromosome 6, from which it is difficult to distinguish. This large group is the one that presents major difficulty in identification of individual chromosomes.
Group 13-15	Medium-sized chromosomes with nearly terminal centromeres ("acrocentric" chromosomes). Chromosome 13 has a prominent satellite on the short arm. Chromosome 14 has a small satellite on the short arm. No satellite has been detected on chromosome 15.
Group 16-18	Rather short chromosomes with approximately median (in chromosome 16) or submedian centromeres.
Group 19-20	Short chromosomes with approximately median centromeres.
Group 21-22	Very short, acrocentric chromosomes. Chromosome 21 has a satellite on its short arm. The Y chromosome is similar to these chromosomes.

711. Sex chromatin. Moore outlined techniques for determination of nuclear sex. Barr reviewed the subject, as did also Ferguson-Smith.

Stewart suggested a theory of the significance of sex chromatin: "In the intermitotic metabolic nucleus the heterochromatin of one X chromosome is apparently necessary for and engaged in the metabolic business of the cell and therefore not stainable. The heterochromatin of any other X chromosomes is, however, superfluous to metabolic requirements, functionally inert at this time, and therefore stainable, usually at the nuclear membrane. This hypothesis would explain the reported findings with respect to sex chromatin in subjects with normal (XX, XY) and abnormal (XO, XXY, XXX) karyotypes." Others have proposed the same or a similar theory.

Riis and Fuchs proposed puncture of the uterus for antenatal diagnosis of fetal sex. They suggested usefulness of the technique in instances where the mother is a demonstrated carrier of a grave sex-linked recessive trait. They envisioned other use in the future, such as the identification of the presence of a gene in the fetus by blood group linkage (linkages yet to be discovered) and the identification of enzyme defects in the fetus. They admit that the procedure

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carries appreciable risk to the fetus and some risk to the mother. The contribution to the management of pregnancy would not seem to justify these risks at present.

Olmstead, Pfeiffer, and Hill found no instance of inconsistent nuclear chromatin pattern among 461 mentally retarded women.

712. Techniques in cytogenetics. Bottura and Ferrari reported that intravenously administered demecolcine (N-desacetyl-N-methylcolchicine) can be useful in the study of human chromosomes. A dose of 0.1 mg. per kilogram of body weight was given intravenously, and a bone marrow determination was made 2 hours later. They stated that in 8 individuals satisfactory results were obtained. The method was also used in studying the chromosomes of malignant cells in ascitic and pleural fluids. The development of methods that utilize peripheral blood makes this possibly hazardous and certainly uncomfortable method with bone marrow aspirations quite unnecessary (Stewart).

Powsner and Berman produced a single photograph of a single cell (in metaphase of mitosis), unstained and without colchicine, from bone marrow. The picture was made within minutes after aspiration. The comforting point was that the number of chromosomes was clearly 46 and the chromosome form was that familiar from material with colchicine added cultured for varying periods of time.

Patau closely examined the methods for identifying specific chromosomes by measurements of length and arm ratio and by pairing. He classed the chromosomes into seven groups in a system essentially identical to the Denver one (Table XIII). He demonstrated that the X chromosome cannot be distinguished from similar size autosomes and that the claim that every pair of homologous chromosomes can be identified cannot be substantiated. Tentatively, he concluded that the X chromosome is in length about 4.8 per cent of the haploid female complement and has an arm ratio of 1.5.

Oliver and Lajtha pointed out reasons why tritium-labeled thymidine is excessively hazardous for in vivo use in man.

A third edition of the useful manual by Darlington and La Cour, *The Handling of Chromosomes*, appeared in 1960. The skin culture technique in man was described by Harnden.

Sex Chromosomes.—

713. The Klinefelter syndrome. Bergman and colleagues studied the chromosomes in 2 patients with chromatin-positive Klinefelter syndrome. In both cases the predominant chromosome number was 47 (44A + XXY). In both cases chromosome numbers above 47 were seen. In one case the deviation from the modal number was especially pronounced; 30 per cent of cells had 48 or 49 chromosomes. In this patient's 48 chromosome cells, there was a small extra chromosome which they felt certain did not represent one of the autosomes in triplicate. They questioned whether it might be a "structurally changed normal chromosome or possibly an inert supernumerary chromosome of the type known as B chromosomes." Nowakowski and co-workers reported chromosome findings.

McLaren reported what she interprets to be an XXY state in the mouse. Only one such animal was observed. The phenotype was male. The mouse died before a critical breeding study could be done. The deduced XXY state was recognized from the male to male, father to son transmission of a sex-linked trait. Nondisjunction in spermatogenesis was inferred.

Lejeune, Turpin, and Decourt found a typical patient with the Klinefelter syndrome with 46 chromosomes. The sex chromosome constitution appeared to be XXY, but in group IV of the autosomes there were only four rather than six and there was an odd large chromosome which appeared to be the result of a reciprocal translocation such that the two long arms of one pair of group IV chromosomes became attached to the same centromere. A surprising feature, assuming the accuracy of this explanation, was the fact that the lack of the short arms of one pair of autosomes had no evident ill effects.

Crooke and Hayward described a patient with chromatin-positive Klinefelter syndrome and XXY/XX mosaicism.

714. Gonadal aplasia. Fraccaro, Kaijser, and Lindsten reported an XO constitution in 2 patients with chromatin-negative Turner syndrome and an XX constitution in 2 chromatin-positive patients. They suggest restricting the term Turner syndrome to the former condition. The karyotype of the parents of one of the XO individuals was normal.

Fraccaro and colleagues described 3 cases of chromatin-positive Turner syndrome in which the patients had 46 chromosomes, one X chromosome, and a long, metacentric chromosome with similarities to the chromosomes of pair 3. They suggested that the last is an "isochromosome"* for the long arm of one X chromosome. If so, the patients are formally trisomic for the long arm and monosomic for the short arm of the X chromosome. What is undoubtedly the identical situation has been found by Ferguson-Smith.

Other patients with chromatin-positive gonadal aplasia who have been studied to date show a puzzling variety of X chromosome anomalies including XO/XX (Ford) and XO/XXX (Jacobs and colleagues) mosaicisms, an apparent XO sex chromosome constitution (Grumbach, Morishima, and Chu, unpublished), and deletions (Jacobs and colleagues) of the X chromosome.

Stewart described a case of chromatin-negative Turner syndrome along with webbed neck and short stature in a 33-year-old person. The patient menstruated from the age of 14 to 20 years. No ovaries were palpated under anesthesia. The patient had severe deuteranomaly. The mother was apparently a heterozygote in that a minor defect was demonstrated in her by anomaloscope and the father had normal color vision. The patient's one X chromosome presumably came from the mother.

Russell and Saylors reported that irradiation of female mice within a few hours after fertilization resulted in an increase in the frequency of XO offspring.

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*An isochromosome (J. Genet. 39:351, 1940) develops during cell division as a result of transverse instead of longitudinal fracture of the centromere. Then, with reciprocal translocation, two chromosomes are formed, each with a median centromere and each with arms which are of equal length and genetically identical.

715. True hermaphrodism. Sasaki and Makino described a patient with true hermaphrodism with 46 chromosomes and an XX sex chromosome constitution, thus confirming the findings of others (¶385). Ferguson-Smith, Johnston, and Weinberg reported on 2 and de Assis and colleagues reported on one case of true hermaphrodism which were, like most (although not all) such cases, chromatin positive. All 3 patients had total counts of 46 and XX sex chromosome constitution. The pathogenesis of true hermaphrodism remains a mystery; testicular differentiation in the absence of a Y chromosome is especially puzzling.

Gordon and colleagues also described a typical true hermaphrodite in whom the karyotype was again that of a normal female. The title, "Chromosome Count in a Hermaphrodite With Some Features of Klinefelter's Syndrome," and the case presentation are confusing since the patient presented typical features of hermaphrodism and none of the Klinefelter syndrome. In the latter condition, micro-orchia is invariably present. In Gordon's case, one testis was "slightly smaller than would be expected." The other testis was undescended, an unusual finding in the Klinefelter syndrome (Bishop and Polani). Gynecomastia, but not complete feminization of the breasts, occurs in the Klinefelter syndrome and hypospadias is not a feature. It should be noted, however, the testicular histologic state in some cases of true hermaphrodism is very similar to that found in chromatin-positive Klinefelter syndrome (Ferguson-Smith, Johnston, and Weinberg).

Hirschhorn, Decker, and Cooper reported a case of what they considered to be true hermaphrodism discovered at birth and the result apparently of XY/XO mosaicism. The buccal smear revealed a chromatin-negative pattern. There was a phallus of about normal size with the urethral opening at its base. There was also a vaginal opening. At laparotomy, the uterus, tubes, and two gonads resembling ovaries appeared normal grossly. Histologically, the gonad showed both follicles containing ova and tubular structures interpreted as early seminiferous tubules. Whereas the bone marrow cells showed the XY/XO mosaicism as stated, the skin cultures showed only the XY sex chromosome constitution. The authors speculated that the Y chromosome was lost in the developing mesoderm. It is probable that this case fits into the category of intersex with undifferentiated gonads (i.e., gonads similar to that of an 8 to 10 week embryo as far as differentiation is concerned) rather than of true hermaphrodism. Gonads of this type are not uncommon in cases of male pseudohermaphrodism.

Bloise and co-workers described an 8-year-old boy with male phenotype but XO sex chromosome constitution. Blood, oral smears, and skin biopsy were chromatin negative. The authors designated it a case of Turner's syndrome. It would seem better considered a case of male pseudohermaphrodism because of the malformation of the external genitals, small phallus with chordae, bifid "scrotum," blind vagina, perineal urethra, ovarian "streak" on one side, and small testis on the other (Martin; Hirschhorn and colleagues). The chromosomes were studied only in the bone marrow. A good possibility of mosaicism exists (XY/XO), as in a case of Hirschhorn, Cooper, and Miller and in a similar case studied in this laboratory. Blank, Bishop, and Caley observed what they interpreted to be XY/XO mosaicism in a 55-year-old chromatin-negative "woman" with primary amenorrhea, short stature, and low intelligence.

Hirschhorn, Cooper, and Miller suggested that many of these cases of true hermaphrodism may prove to be XXY/XX mosaicism when the chromosomes of more tissues are studied. The suggestion was based not on evidence so far available but on faith that a Y chromosome is necessary for the formation of testicular tissue.

716. The triple X syndrome. Jacobs and her associates described 3 cases of abnormality involving the X chromosome. All patients were phenotypically female. One, a "superfemale" (XXX), menstruated regularly. The possibility of fertility in such individuals raises the further possibility of the production of XXX or XXY offspring through secondary nondisjunction. In a second patient, seen for primary amenorrhea, there was deletion of part of one X chromosome. The sex chromatin pattern was positive, but the chromatin mass was small and only 7 per cent of cells showed chromatin. In a third patient, age 52, with primary amenorrhea and angina pectoris, there were two sex chromatin masses, low-normal intelligence, and two cell lines compatible with XXX/XO mosaicism.

Stewart and Sanderson reported on a 35-year-old woman of reduced intelligence who is a triple X female and has borne 4 children (she was again pregnant at the time of report). These cases obviously raise the possibility of a familial occurrence of chromosomal aberrations through secondary nondisjunction.

Lennox, like others, questioned the clinical appropriateness of the term superfemale and suggested that specific designations based on karyotype, such as "triple X" or, for Mongolism, "22-trisomy" might be used instead. (In the numerology of many workers, Mongolism is a "21-trisomy." Furthermore, following the convention now well established by the Drosophila workers, "triplo-21" would be the preferred designation.)

Fraser and colleagues performed a nuclear sex survey of 595 women in an institution for mental defectives. Four cases of double sex chromatin resulting from the triple X syndrome were discovered. After the Klinefelter syndrome, the triple X syndrome is probably the most frequent sex chromosome anomaly.

De Carli and colleagues described a woman with what they considered to be a trisomic condition of a large autosome. Since there was double sex chromatin, the case is probably one of the triple X syndrome (Court Brown and colleagues). The same type of case and the same interpretation (almost certainly misinterpretation) was published by Sandberg and colleagues. A small deletion in one X chromosome could account for the difficulty in matching the three X chromosomes in certain of these cases.

717. The triple X–Y syndrome. Ferguson-Smith, Johnston, and Handmaker described 2 patients with a new sex anomaly, the triple X–Y syndrome: primary amentia and micro-orchidism associated with an XXXY sex chromosome constitution. The total chromosome count was 48. Many cells of all tissues examined showed double sex chromatin. The testicular histologic state was like that of the Klinefelter syndrome. However, mental retardation was of much more severe degree than is usually seen in the Klinefelter syndrome. The mothers had normal sex chromatin pattern. Nondisjunction in gametogenesis in both parents is a

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possible, although perhaps not the most likely, explanation. More plausible is nondisjunction occurring in both meiotic divisions of oogenesis. Barr and Carr confirmed the clinical and cytologic descriptions of the triple X–Y syndrome.

718. The double XY syndrome. Muldal and Ockey described a patient with chromatin-positive Klinefelter syndrome with 48 chromosomes and the sex chromosome constitution XXYY. "Double male" was the designation applied but is probably as inappropriate as "superfemale." It was suggested that in the father both X and Y passed into some of the product cells from the first meiotic division and that some XYY sperm resulted from the second division. The same sex chromosome constitution has been observed by Barr and Carr.

719. Other sex chromosome anomalies. Barr and Carr have observed persons with three sex chromatin masses and XXXX sex chromosome constitution.

Fraccaro, Kaijser, and Lindsten described a 7-year-old boy with 49 chromosomes. Clinical features were peculiar facies, protruberant abdomen, congenital heart malformation, kidney malformation, mental retardation, right undescended testis, and divided scrotum with penis. The first interpretation of the chromosome complement was that it represented, in addition to XXY sex chromosome constitution, trisomy of chromosomes 8 and 11. However, Fraccaro and Lindsten later studied sex chromatin in the buccal smears and found a modal number of three. Since the usual experience has been that the number of chromatin masses is one less than the number of X chromosomes, they revised their interpretation to the view that their patient was of XXXXY constitution. (They referred to a personal communication from Jacobs and colleagues concerning the observation of an XXXXY/XXXY mosaic by the Edinburgh group.) The above experience indicates the necessity of buccal smears in connection with chromosome studies.

A general discussion was given by Harnden.

The Autosomal Chromosomes.—

720. Mongolism. Penrose (J. Ment. Sc. 97:738, 1951) concluded that in instances where more than one case of Mongolism occurs in a family, maternal age is not a factor and the transmission appears to be through the mother. The work of Snell, Bodemann, and Hollander (1934) on hereditary malformations in mice suggested chromosomal translocations as a mechanism in such cases. Penrose, Ellis, and Delhanty found in a 48-year-old Mongoloid patient what they interpreted to be a reciprocal translocation of chromosomes 21 and 22. The total count was 46. Most interesting was a pair of siblings, male and female Mongoloids, also with a chromosome complement of 46. However, there was an odd chromosome interpreted as a fusion of major portions of chromosomes 15 and 21. Furthermore the mother, maternal grandmother, and a normal sister all showed the same peculiarity: 45 chromosomes with an odd large chromosome and one chromosome 21 missing.

The proposed explanation for the last pedigree is that a reciprocal translocation involving chromosomes 15 and 21 had occurred in an ancestor on the

maternal side. A centric fragment was later lost, and the large fused chromosome was transmitted through several generations of normal individuals. The normal individuals can produce unbalanced gametes with an excess or deficit of chromatin in the pairs involved. It is suggested that the 2 Mongoloid siblings resulted from fertilization by normal sperm of unbalanced ova containing nearly double quantities of chromosome 21—the regular chromosome 21 and that portion carried on chromosome 15.

In 1960 evidence suggesting translocation was found in Mongoloid individuals also by Polani and colleagues, by Fraccaro, Kaijser, and Lindsten, and by Carter and associates. The last group found 3 Mongoloid persons (2 siblings and a maternal cousin) had occurred in the family. The one surviving had 46 chromosomes—two chromosomes 21 and one chromosome which appeared to be a combination of most or all of chromosomes 15 and 21. Thus the patient was essentially trisomic for chromosome 21. The two mothers of Mongoloid children (sisters) had 45 chromosomes, with only one chromosome 21, including an abnormal 15-21 chromosome—the equivalent of a normal complement. The maternal age in these cases was not advanced.

Lejeune brought up to date all the relevant studies on Mongolism in an extensive review. He suggests that Mongolism is the first example of a defect in metabolism caused by *excess* of an enzyme which is the direct result of trisomy. In favor of this he refers to preliminary studies on tryptophan metabolism in Mongolism, particularly to the finding of high levels of urinary 5-hydroxyindoleacetic acid.

Fraccaro, Kaijser, and Lindsten described a male Mongoloid child with 46 chromosomes. There were only four short acrocentric chromosomes rather than the normal five of the male, and an extra chromosome similar to those of pairs 19 and 20 was present. It was thought that the Mongoloid child might be trisomic for chromosome 19 and monosomic for chromosome 21.* An alternative possibility was that the extra chromosome was the product of a translocation from one chromosome 21 to the other. The father of the child, 58 years of age at the time of birth of the child and apparently in good health, had 47 chromosomes. He was probably trisomic for chromosome 19. The observations, confusing as they may be to interpret, do indicate (1) that chromosomal abnormalities can exist in fertile, healthy persons and (2) that the Mongolism syndrome can result from chromosomal aberrations other than trisomy of chromosome 21.

Polani and others also found a female patient with Mongolism with 46 chromosomes, including only four small acrocentric chromosomes, as is normal for the female. There were only five (rather than six) of the longer acrocentric ones (groups 14, 15, and 16), but an additional unmatched chromosome probably in group 15 was found. The authors suggested that a translocation from chromosome 22* to chromosome 15 had occurred. The child was being studied because the mother had been only 21 years old at the time of the patient's birth.

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*Polani, Ford, and others count the X chromosome(s) as set 6, making 22 the set which is trisomic in the usual case of Mongolism. Fraccaro's numerology is confined to the autosomes, and set 21 is, by his system, the one involved in Mongolism. The group of Lejeune and Turpin, on the other hand, divides the autosomes into rod-shaped, J-shaped, and V-shaped forms, designating them accordingly, and indicates V_h as the set involved in Mongolism.

German and Bearn found no chromosomal abnormality in the parents of 2 Mongoloid individuals.

Harnden, Miller, and Penrose reported further on the 45-year-old man with the Klinefelter-Mongolism type of double aneuploidy—a case now famous, having been reported early in the development of pathocytogenetics in man (¶382). They point out that judging from the frequency of the separate states (about one in 700 for Mongolism and one in 800 for the Klinefelter syndrome), the frequency of the coincidence should be about one in 560,000 births. However, the existence of genes predispositional to nondisjunction would tend to increase the frequency of double aneuploidy, and a reduced viability of the double aneuploid fetus would tend to reduce the frequency.

Lanman and colleagues described a 10-month-old Mongoloid idiot with the Klinefelter syndrome. Chromosome analysis revealed 48 chromosomes and a combination of the usual features of both syndromes. Lehmann and Forssman likewise described the combination of Klinefelter syndrome and Mongolism. Of interest is the fact that although the buccal smear was chromatin positive and the sex chromosome constitution was XXY by chromosome analysis, the study of neutrophils showed chromatin negativity. (See ¶853 for comments on the same paradox in some cases of the Turner syndrome. Whether mosaicism is the basis is being studied.)

Hanhart described a Mongoloid woman who produced 2 Mongoloid offspring. In an appended personal communication, Hanhart reported that Delhanty, under Penrose's direction, had demonstrated the typical trisomy both in the mother and in one of the children. Johnston, in this laboratory, also demonstrated 47 chromosomes in the Mongoloid child of a Mongoloid woman. These, both still unreported, are probably the only two instances of apparent secondary nondisjunction found thus far in man.

721. Other autosomal aberrations. Two and possibly three new autosomal trisomic syndromes were described. No autosomal monosomy has been described. Deficiency of a chromosome probably is more disruptive than the presence of an additional chromosome. Furthermore, trisomy of none of the twelve largest autosomes has been described. Probably such a relatively large portion of the genetic material is contained in the large autosomes that the effect of trisomy is prohibitively disruptive and is lethal at an early stage. The patients described by De Carli and colleagues, by Sandberg, Crosswhite, and Gordy, and by Fraccaro and colleagues as having trisomy of one of the largest autosomes are, in the opinion of most, instances of the presence of three (or more) X chromosomes.

Edwards and colleagues described an extra chromosome identical to pair 17 (by Ford's nomenclature, which assigns number 7 to the X chromosome). The infant showed peculiar facies (oddly shaped skull, low-set and malformed ears, triangular mouth with receding chin), webbed neck, shieldlike chest, webbing of the toes, ventricular septal defect, mental retardation, and neonatal giant cell hepatitis. The last is of interest in connection with the work of Fienberg (¶738), who interprets this disorder (also called perinatal idiopathic hemochromatosis) as the result of an inborn error of metabolism. Review of the

Fig. 31.—Group IV (also known as group D) autosomal trisomy.

A. *B.*

Figs. 31*A* and 31*B*.—This newborn female infant (A. S., 975712) weighing 2,355 grams shows microcephaly, anophthalmos, malformation of the ears, nose, and brain, and ventricular septal defect.

Fig. 31*C*.—Also present were polydactyly and flexion deformity of the fingers.

literature suggested to the authors that the syndrome in this infant may have been encountered before. The identity of some of the features to some of the somatic features of gonadal aplasia (Turner syndrome) is noteworthy. It appears that an extra autosome in the seventeenth set may produce some of the same imbalance as does a missing X chromosome. An alternative interpretation of the

cytologic findings in this case is that the extra chromosome is an X chromosome which has undergone deletion (as in the case of Jacobs and associates) and that the diagnosis is chromatin-positive Turner's syndrome. The histologic demonstration of normal ovaries is not a bar to this diagnosis, since fertility is now recognized as a rare occurrence in association with this syndrome.

Patau and colleagues described an infant with an extra medium size acrocentric autosome in their "group D" (13-15, group IV). (The Wisconsin workers believe that the chromosomes can be grouped into seven classes, A through G, but that features are not sufficiently distinctive to permit further identification with certainty from case to case.) The chromosome involved in this syndrome (15 in the numerology of some workers) is apparently distinct from that in the syndrome of Edwards and co-workers. The congenital defects were cerebral defect, anophthalmos, cleft palate, harelip, simian creases, "trigger thumbs," polydactyly, capillary hemangiomata, and heart defect. Up to April 29, 1960, 6 cases of this trisomy had been discovered and studied. (See Fig. 31 for a case studied in this laboratory.)

Smith, Patau, and colleagues also described 2 patients with trisomy of a group E chromosome (either 17 or 18). These persons showed anomalies of the ears, spasticity, "rocker bottom" feet, flexion deformity of the fingers, micrognathia, umbilical hernia, congenital heart disease, and mental retardation.

In a patient with the *Sturge-Weber syndrome*, Hayward and Bower found trisomy of what they thought to be chromosome 22. In part the study was sug-

Fig. 31*D*.—The chromosome count was 47, with an XX sex chromosome constitution and an extra autosome in group IV (or D).

gested by the fact that hemangiomata occurred in the trisomy of chromosome 15 reported by Patau and colleagues of Wisconsin. In 3 cases studied in this laboratory and in cases studied elsewhere (e.g., Lehmann and Forssman), it has not been possible to confirm the finding of an abnormal karyotype in the Sturge-Weber syndrome.

722. Neoplasia. Bayreuther stated that Theodor Boveri (¶671) first aroused interest in the chromosome constitution of tumor cells. He reviewed studies of chromosomes in spontaneous, untreated primary tumors in mice, cattle, and man. The majority showed a normal karyotype. Virus-induced, chemically induced, and irradiation-induced tumors likewise were usually normal. "The results reported are inconsistent with the chromosome mutation theory of carcinogenesis." Normal DNA values support the chromosome data. There is "little correlation between the mutagenic and carcinogenic activity of tumor-inducing agents." Chromosomal aberrations observed are, he thinks, the result of events separate from the primary malignant change. They may, he grants, contribute some advantage to cancer cells when they occur.

Ishihara and Makino studied the chromosomes in the ascitic fluid in 4 patients with Laennec's cirrhosis and in the pleural fluid in 4 patients with tuberculosis. The karyotype was normal in all cases. They suggested that the technique of chromosome study might be useful in differentiating cancer as the cause of effusion. Clearly, only positive findings, that is, findings indicative of cancer, could be relied on; "negative" findings would mean little.

Tough and colleagues reported chromosomal changes in cells cultured from the peripheral blood of persons who received x-ray treatment to the spine for ankylosing spondylitis a few days previously. Changes consisted of breaks with formation of fragments, ring chromosomes, and dicentric chromosomes. In the same article, the authors reported normal chromosome counts in 15 patients with eleven conditions including arthrogryposis, anophthalmos, the Pelger-Huët anomaly, and others.

In cases of chronic granulocytic leukemia, Nowell and Hungerford described what they interpreted to be a deletion of one of the 4 smallest autosomes. Earlier, when only male patients had been studied, these workers had the impression that it might be the Y chromosome which was defective. Like others, they found no abnormality in acute leukemia.

Baikie and colleagues described the same anomaly, which they suggest may be a specific chromosomal abnormality in chronic myeloid leukemia of man: one of the four smallest acrocentric chromosomes is unusually small and appears to have suffered a deletion. In most Mongoloid persons, there is a morphologic abnormality, a deficiency in nuclear lobulation, of the polymorphonuclear leukocytes. The authors pointed to the fact that acute (not chronic) leukemia occurs at relatively high frequency in association with Mongolism. Since the autosome implicated in the deletion of chronic myeloid leukemia may be the same as that involved in the trisomy of Mongolism, they suggest that the autosome "may possess a locus or loci concerned with some aspect of the control of leucopoiesis." The abnormality was found in blood cultures but not in skin cultures.

Leukemia was also studied by Sandberg and colleagues and by Ford. Hale and Wilson studied the DNA content of the nuclei of leukemic leukocytes.

Studies of polyploidy in human tumors were reported by Atkin and Ross. Revész and Norman studied the relation between polyploidy and radiosensitivity of tumors.

723. Miscellaneous. Böök and Santesson described a malformation syndrome in a triploid individual (with 69 chromosomes). The one-year-old male child showed retardation of physical and mental development, porencephaly, micrognathia, localized lipomatosis of the back of the hands, feet, and thighs, bone syndactyly, and ataxia. The chromosome complement was found to be 3A + XXY in over twenty-five cells from an 11 day skin culture. Confirmation of this preliminary report is awaited with great interest.

Stern described a mosaic in Drosophila consisting of X, XX, and XXX tissue and explained its origin by mitotic nondisjunction. The sex chromosome constitution was inferred from the state with reference to certain X-linked traits affecting various body tissues.

A study of overripe eggs of the rat by Witschi gave first results which suggest that nondisjunction of diads occurs rather frequently in the second meiotic division.

The diploid chromosome number of nine chimpanzees (*Pan troglodytes*) was determined to be 48, with a probable sex chromosome constitution of XX-XY (Young and colleagues).

TABLE XIV

	BLOOD GROUP PERCENTAGES				GENE FREQUENCIES		
	O	A	B	AB	p	q	r
Diploid	48	41	8	3	0.69	0.25	0.06
Trisomic	33	50	9	8			

By an extension of the Hardy-Weinberg law, Bateman estimated the ABO blood group distribution to be expected in a group of persons trisomic for the chromosome or part of a chromosome bearing the ABO blood group locus. For the normal diploid state, the frequencies of the several genotypes (OO, OA, OB, AA, AB, and BB) are given by the terms in the expansion of the expression $(p + q + r)^2$. For the trisomic state this expression becomes $(p + q + r)^3$. The expected frequencies of the trisomic genotypes OOO, OOA, OAA, AAA, OOB, OBB, BBB, OAB, AAB, and ABB are, respectively, p^3, $3p^2q$, $3pq^2$, q^3, $3p^2r$, $3pr^2$, r^3, $6pqr$, $3q^2r$, and $3qr^2$. The only genotype directly identifiable is OOO (p^3). The other phenotypes have three possible genotypes. Note that whereas in the diploid the AB phenotype and genotype are identical, in the trisomic three genotypes correspond to the AB phenotype. Using gene frequencies from the Manchester region, Bateman provided the interesting comparisons shown in Table XIV.

Finally, Bateman quoted Steward's data on ABO blood group distributions in childhood tumors of ectodermal origin, mostly gliomas, with a few instances of retinoblastoma, and tumors of the sympathetic nervous system and epithelium. The blood groups were significantly different from the normal diploid expectation but were consistent with trisomy for the ABO locus. Bateman urged cytogenetic investigations of this group.

VII. BIOCHEMICAL GENETICS

724. General discussions were provided by Guest, Landing, Bearn, Riley and Kirkman, Hsia, and others. Inherited variations in the metabolism of aromatic amino acids (alkaptonuria, tyrosinosis, phenylketonuria, Hartnup disease, maple syrup urine disease, and others) were discussed by Sutton and Tashian. Gerrard and Marko gave a general review and discussed specifically glycogen storage disease, pentosuria, glucose-6-phosphate dehydrogenase deficiency, galactosemia, phenylketonuria, alkaptonuria, maple sugar urine disease, hyperoxaluria, argininosuccinic aciduria, Hartnup disease, congenital adrenal hyperplasia, goitrous cretinism, hypophosphatasia, Wilson's disease, pseudocholinesterase deficiency, and glucuronyl transferase deficiency. Aminoaciduria was discussed by Berry, by Chisolm and Harrison, and by Ghadimi and Shwachman.

Hsia reviewed the evidence on biochemical detection of heterozygous carriers of recessively inherited diseases: acatalasemia, Crigler-Najjar hyperbilirubinemia, galactosemia, von Gierke's disease, hypophosphatasia, and others.

Papers on biochemical genetics published in *Federation Proceedings* included contributions by Hotchkiss and Evans (fine structure of a genetically modified enzyme), Bonner, Suyama, and DeMoss (genetic fine structure and enzyme formation), Larner (glycogen metabolism), Touster (essential pentosuria), Kalckar (galactose metabolism), Mills (polysaccharide synthesis in the pneumococcus), and Carson (glucose-6-phosphate dehydrogenase deficiency).

725. Abetalipoproteinemia. Salt and five colleagues enlarged on the acanthocytosis syndrome (¶'s 204 and 464). Retinopathy (atypical retinitis pigmentosa) and neurologic dysfunction (especially ataxia) occurred in the 4 previously reported patients. The red cells were spine covered; hence the name acanthocytosis. Scrutiny of the reports shows also that all 4 had the celiac syndrome. In the study of a 17-month-old girl with steatorrhea, the authors found that there was no serum betalipoprotein. Serum cholesterol level was 22 mg. per 100 ml. and phospholipid level 45 mg. per 100 ml. The red cells showed acanthocytosis. Both parents and one grandparent showed hypobetalipoproteinemia. They suggested that the condition be termed abetalipoproteinemia and that it is an inborn error of metabolism with a recessive mode of inheritance. Whether the retinopathy and nervous system damage are secondary to prolonged deficiency of vitamin A (or another fat-soluble vitamin) may be elucidated by the results of water-soluble vitamin A supplementation in this patient. The mechanism of the steatorrhea is not clear.

Mier, Schwartz, and Boshes described a similar case in a 17-year-old Jewish boy who had had the celiac syndrome in childhood and who subsequently developed retinal changes and progressive ataxic neuropathy. He showed acanthocytosis (¶464) and hypocholesterolemia. Webbing of the neck was present. They persisted in using the improper term acanthrocytosis (instead of acanthocytosis). All reported patients known to them had also been Jewish.

726. Acatalasemia. Takahara and colleagues analyzed cases of hypocatalasemia, the genetic carrier state of acatalasemia, an autosomal recessive disease

which has been detected only in Japan. The pedigree data were with one exception completely consistent with the recessive hypothesis; in one family an acatalasemic member had entirely normal relatives including offspring, siblings, and offspring of siblings. Hypocatalasemia has no apparent clinical effect. The seventeen affected families are widely distributed in Japan. Consanguinity of some degree was found in all families but one. The frequency of affected homozygotes was estimated at 0.000021 and of heterozygotes at 0.005958. It was estimated that about 1,800 persons in Japan have acatalasemia and about 500,000 persons are hypocatalasemic. These estimates were made (with certain assumptions) on the basis of the well-known relationship

$$q = \frac{c(1 - k)}{16k - 15c - ck},$$

where q is the frequency of the gene which in homozygous states results in acatalasemia, k is the proportion of first cousin marriages among the parents of affected persons, and c is the proportion of first cousin marriages in the general population. This heterozygous carrier state is one of the very few in which, by the chemical methods available, there is no overlap between the characteristic (in this case, enzyme level) in heterozygotes and homozygotes (¶391).

727. Agammaglobulinemia. Kushner and colleagues reported on what appears to be a new variety of hypogammaglobulinemia inherited as an autosomal recessive trait. The proband had hypogammaglobulinemia, splenomegaly, and leukopenia and died of disseminated histoplasmosis. Three of his 6 children (one boy, 2 girls) had hypogammaglobulinemia, splenomegaly, leukopenia, and increased susceptibility to infection. The father of the proband had only splenomegaly.

Good and Page described a case of sex-linked recessive agammaglobulinemia with death from viral hepatitis.

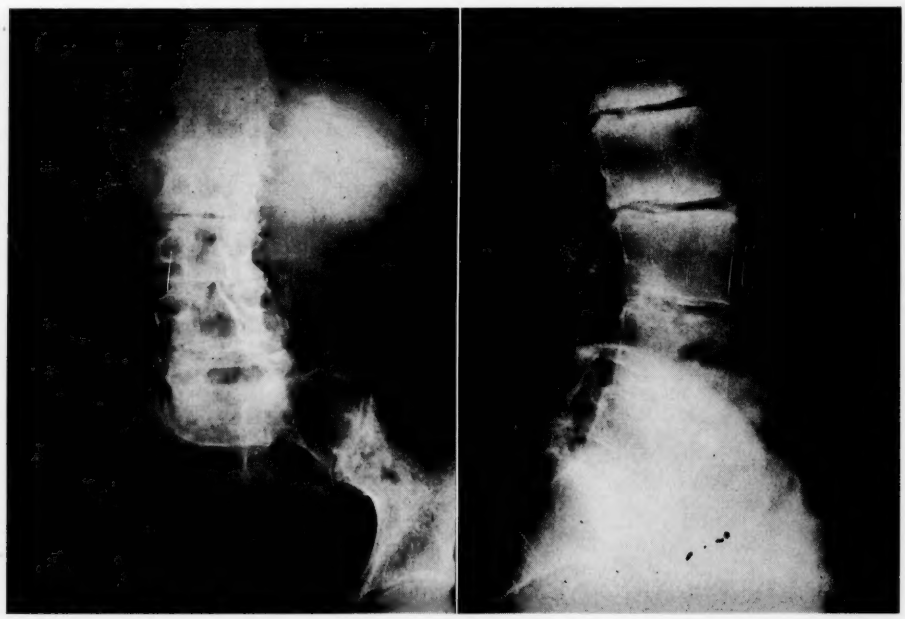
728. Albinism. In Northern Ireland, Froggatt estimated that he achieved 80 per cent complete ascertainment of cases of classic albinism using these criteria: hypopigmented fundus oculi, congenital nystagmus, and abnormally translucent irises in a person with white, flaxen, or fair hair from birth. The completeness of ascertainment was judged by the number of cases ascertained only when the family of an albino was investigated. Ascertainment was poorer in higher social classes, older age groups, and families with small numbers affected. The family data in all respects support the autosomal recessive hypothesis. A phenotype frequency of about one in 10,000 was estimated. First cousin marriages occurred in 4.5 per cent of the parents, a finding in favorable agreement with the 5.3 per cent predicted from Lenz's formula. In eighty-nine sibships on which satisfactory data were available, there were 138 albinos (81 male and 57 female) and 259 unaffected siblings (140 male and 119 female). A male excess has been noted in other data. Almost all the male excess was in the propositi and the sex ratio of secondary cases was about 1, suggesting that the male excess is a bias of ascertainment. The mutation rate was estimated to be between 3.3 and 7×10^{-5} per gene per generation. Using a method of transillumination of the eye, Froggatt

studied the intensity of iris pigmentation in 57 parents and 6 children of albinos in the age range (21 to 70 years) in which incomplete development and senile atrophy could be anticipated to have little effect. Abnormal iris translucency was judged to be present in about 70 per cent, a proportion significantly higher than in a control group. Partial expression in the heterozygote was suggested.

729. Albumin abnormalities. Williams and Martin described acrocyanosis in association with *bisalbuminemia* in a grandfather, father, and son. Some other members of the family had bisalbuminemia without acrocyanosis. The son's fingers could not be fully extended. "It seems almost as if the skin no longer fits his fingers." Wieme studied a family with seven instances of bisalbuminemia in two generations.

Humphrey also demonstrated very low but existent levels of serum albumin in a case of *analbuminemia*, thereby providing a possible explanation for the failure of affected persons to develop antibodies to infused human albumin.

730. Alkaptonuria. Cases and families were reported by Rones, by Abe and colleagues, and by DiFiore, among others. Natarajan discussed the arthritis involved (Fig. 32). Wagner and colleagues described a case of ochronosis with coronary thrombosis and prostatic calcification. (In 1944 Hugh Young, a famous urologist, reported on pigmented prostatic calculi with alkaptonuria.) Hendel and Ben-Assa had 2 cases of urolithiasis.



A. *B.*

Fig. 32.—*A* and *B*, Ochronotic arthritis in a 34-year-old man with alkaptonuria (R. S., 761270).

Milch reported in detail on eight highly interrelated kindreds in the Dominican Republic. A quasidominant inheritance was the result of much inbreeding. Closer analysis revealed that the pedigree pattern was consistent with recessive inheritance (¶394). Studies bearing on ochronotic arthropathy were reported by Milch and Robinson.

731. Cystinosis. Korn demonstrated cystine crystals in the peripheral white blood cells of a patient with cystinosis.

732. Fructose intolerance. A new inborn error of metabolism inherited as an autosomal recessive trait, fructose intolerance was described by Prader and his associates. The primary enzyme defect concerns, it was suggested, 1-phosphofructaldolase. The clinical symptoms are due, at least in part, to the hypoglycemia caused by the accumulation of fructose-1-phosphate which leads to competitive enzymatic inhibitions of the glycolytic pathway.

733. Galactosemia (Kalckar). Kirkman reviewed all aspects of the disease, including the procedures currently used in the study of galactosemia: three methods for study of urinary galactose, the galactose tolerance test, and four tests involving erythrocytes. Donnell, Bergren, and Cleland also gave a review.

Segal, Pesch, and Topper found in 3 prepubertal patients with galactosemia that administration of progesterone considerably increased galactose metabolism as indicated by the proportion of C^{14} label which appeared in the expired air as $C^{14}O_2$. Furthermore, in rats, partial protection against galactose cataract was afforded by progesterone.

Using normal and galactosemic human leukocytes, Weinberg and Segal were unable to find a specific inhibition of glucose oxidation via the hexosemonophosphate pathway, even with conditions resulting in greater accumulation of gal-1-P than was recorded in experiments in which lenses from galactose-fed rats were used (Lerman). (See ¶401.) Patterson examined experimentally two theories of the mechanism of manifestations in galactosemia: (1) that there is interference with glucose metabolism by accumulated intermediaries of galactose metabolism and (2) that essential amino acids are lost in the urine because of damage to the renal tubule. In rats fed high galactose diets, clinical effects can be modified by supplementation with glucose, fructose, and "nonessential" amino acids. These findings Patterson interpreted as supporting the first theory.

Dawson, Hickman, and Kelley performed a genetic study of galactosemia in four generations using assays for galactose-1-phosphate-uridyl transferase. Heterozygotes were identified and the resulting pedigree pattern supported the recessive hypothesis.

Hsia and colleagues reported further studies of heterozygous carriers of galactosemia using four methods of assay. All have some overlap between the groups of heterozygotes and homozygous normal persons. Donnell and colleagues also discussed detection of heterozygotes.

Schwarz presented an improved method for estimating gal-1-P in erythrocytes and proposed it as a method for following the adequacy of treatment.

The specific defect involves the conversion of galactose-1-phosphate to glucose-1-phosphate.

Krooth and Weinberg studied cells cultured from the skin of 2 galactosemic homozygotes, one heterozygote, and 5 normal homozygotes, also cells cultured from the bone marrow of a galactosemic homozygote and a normal homozygote. Galactosemic and normal cells grew at the same rate when the hexose in the medium was glucose. When galactose was substituted, the galactosemic cells grew no more than they did when no hexose was provided.

Cordes reviewed the subject of galactosemic cataract.

734. Glucose-6-phosphate dehydrogenase deficiency. Larizza, Brunetti, and Grignani gave a long review of "enzymopenic hemolytic anemia." Carson also gave a useful review.

Brewer, Tarlov, and Alving suggested the use of a methemoglobin reduction test in population studies.

In Nigeria, Gilles and Ikeme pointed out that "black water fever" is frequently drug-induced hemolytic anemia in persons with the defect of G-6-P D.

Szeinberg and colleagues described aspirin as the agent precipitating hemolytic anemia in an Iraqi Jew with this defect.

Alving and his colleagues described mitigation of the hemolytic effects of primaquine in persons deficient in G-6-P D by intermittent regimens for administration of the drug. Since young cells are much less sensitive or not sensitive at all, a fully compensated hemolytic process can be achieved by proper dosage. The observation that in favism acute hemolytic episodes are spotty in occurrence among persons exposed to the fava bean has led to the suggestion that a further factor such as allergy might be involved (¶402). In fact, low grade persistent exposure may be responsible for the failure of attacks to occur in susceptible persons. The occurrence of increased reticulocytosis without anemia in the Sardinian populations studied by Siniscalco would suggest such a mechanism.

Gower and Frommer described acute favism in a 3-year-old Cypriot boy living in England. The authors cite Larizza and coauthors (1958) as having demonstrated the primaquine-sensitive defect of the erythrocyte in favism. Zinkham, Lenhard, and Childs (1958), Gross, Hurwitz, and Marks (1958), Szeinberg and Sheba (1958), and Ventura, Grignani, and Brunetti (1958) have also demonstrated the defect by glutathione-stimulating hormone stability test and by assay of G-6-P D.

Roth and Frumin studied the effects of fava bean extracts in vitro. The erythrocytes of a 2-year-old girl with favism underwent hemolysis when exposed to the extracts. Normal serum or plasma inhibited the hemolysis. The serum of the girl did not. Serum from the father of the patient, although he displayed the G-6-P D defect of the erythrocytes, had normal hemolysis-inhibiting effects.

Weatherall described three Malay families in which G-6-P D deficiency was associated with severe hemolytic disease of the newborn, resulting in kernicterus. In each case ABO and Rh incompatibility, infection, and hemoglobinopathy were excluded, and, so far as possible, drug sensitization was also excluded. G-6-P D deficiency is uncommon in Malaya as is also the Rh-negative state. The pro-

bands in these families were the only instances of hemolytic disease of the newborn in 600 Malay births in the British Military Hospital, Singapore, between 1957 and 1959. The environmental factor precipitating the hemolysis, if any such factor exists, is unknown.

Smith and Vella presented evidence that the unexplained kernicterus seen in many full-term infants in Singapore is due to the G-6-P D defect of the erythrocyte. Among newborn Chinese males in Singapore the defect occurs in about 2.6 per cent, whereas in newborn Indian males the frequency is about 4.7 per cent. However, kernicterus on this basis occurs almost exclusively in Chinese. "It is therefore probable that the factor precipitating hemolysis is related to traditional Chinese methods of caring for the mother and baby during the puerperium." The presenting symptom was severe jaundice which often killed before the hemoglobin had fallen very low. Immaturity of the neonatal liver was thought to be responsible for the latter fact.

In Athens, Doxiadis, Fessas, and Valaes likewise found low levels of enzyme in 14 out of 17 cases of severe and otherwise unexplained neonatal jaundice. Of the 14, 13 were in males. Exchange transfusion was used in the treatment of these patients.

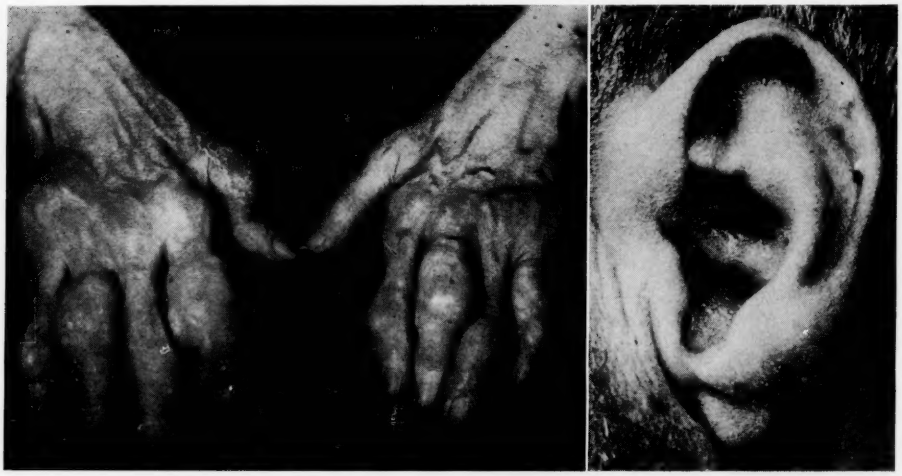
In Italy, Panizon studied 19 jaundiced neonates with unstable glutathione and/or G-6-P D deficiency. Rarely was a precipitating factor found, but in many cases evidence of hepatic impairment was noted. Penizon suggests the latter may be due to the enzyme deficiency. However, of his 19 patients, 8 were female.

In the male Bantu of western Congo, Sonnet and Michaux found a frequency of G-6-P D deficiency of 21.5 per cent. The frequency of sickle trait was 21.8 per cent. Data on Rh and ABO blood groups and on haptoglobin types were also given. The authors spoke repeatedly of linkage and lack of linkage between these several traits. It is not true genetic linkage they mean, although they seem to think so.

Ramot and colleagues found that in non-Ashkenazi Jews with primaquine sensitivity, the saliva contains low amounts of G-6-P D, there being no overlap with the normal individuals in their series. The report extends the findings of this group that, unlike the situation in affected Negroes, the defect extends to tissues other than the erythrocyte. Furthermore it provides a method which will possibly be useful in surveys.

Kirkman, Riley, and Crowell studied the characteristics of G-6-P D from a case of nondrug-induced, chronic nonspherocytic hemolytic anemia of Caucasians in which this enzyme activity is low. A qualitative difference in the enzyme from that of normal persons and that of persons with primaquine sensitivity was demonstrated. Specifically, much greater lability without stabilization by low concentrations of TPN was characteristic of the G-6-P D from nonspherocytic hemolytic anemia. Although the heat of inactivation of enzymes from three sources (normal Caucasian, Caucasian hemolytic anemia, and Negro primaquine sensitivity) was essentially the same, striking differences in Michaelis constants and pH optima were observed between hemolytic anemia enzyme on the one hand and primaquine sensitivity and normal enzyme on the other.

Fig. 33.—Valvular heart involvement in gout. A 52-year-old patient (P. L., 692250) with severe tophaceous gout has a loud mitral systolic murmur. Tophi of the mitral leaflets are possible.



A. *B.*

Fig. 33*A* and 33*B*.—Marked tophaceous changes in the hands; tophi of the pinna.

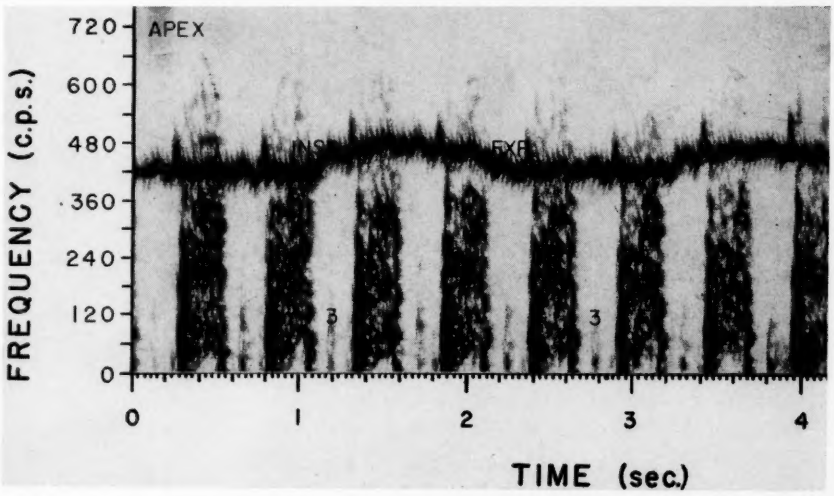


Fig. 33*C*.—Spectral phonocardiogram of auscultatory findings at apex. The holosystolic murmur (*SM*) and the third heart sound (*3*) are consistent with mitral regurgitation.

The failure to demonstrate a difference between the enzymes of normal and of primaquine-sensitive individuals is consistent with the report of Rimon and colleagues that there is normally an activator for human erythrocytic G-6-P D and that it is this activator, not the enzyme itself, which is defective in primaquine sensitivity.

735. Glycogen storage disease (Larner; Stetten and Stetten). Yamamoto and colleagues described the first case of glycogen storage disease of the heart discovered in Japan. The parents were first cousins, and 3 out of 5 siblings of the proband had died of unknown cause in the first year of life.

Lowe and colleagues found a clotting defect in each of 6 children with liver glycogen disease and in at least one parent of each. The demonstration in the presumed heterozygous carrier is of particular interest.

Calderbank and colleagues studied material from 2 siblings with glycogen storage disease. In one, the defect seemed to be of "type 3" and a deficiency of the "debrancher" enzyme was inferred because an abnormality of outer chain length of glycogen was discovered. In the other sibling, however, liver glycogen had a normal structure but glucose-6-phosphatase activity was greatly diminished suggesting that the disease was of "type 1" in this sibling. The findings are distinctly perplexing.

Howell, Ashton, and Wyngaarden pointed out that lipid and purine metabolism, as well as carbohydrate metabolism, is disturbed in von Gierke's disease.

736. Gout. Wyngaarden suggested that there is evidence in gout both for an increased rate of uric acid synthesis and for an impaired net elimination by the kidney. Gutman also discussed gout as an inborn error of metabolism.

Duncan and Dixon reported a family, with 8 children from parents both of whom were hyperuricemic. The proband, a 19-year-old man, had severe renal hypertension and mild gout. A sister had died at the age of 14 years of hypertensive renal failure. The mother and 2 sisters had hypertension and pre-eclamptic toxemia. Two brothers, ages 23 and 15 years, had albuminemia and elevated blood urea level. Yet another brother developed gouty deposits and elevated blood pressure. "Familial hyperuricemia should therefore be considered as a possible cause of renal hypertension, particularly in young people, even in the absence of gout." Improvement of renal function with administration of probenecid was claimed.

Emerson observed two families with gout in which homozygosity for the responsible gene may have occurred. In one, asymptomatic hyperuricemia occurred in both parents of a patient with gout of extreme degree and rapid progression. The only relative with clinical gout was a cousin of the mother. In the second family, gout or hyperuricemia could be traced through five generations. From the union of a gouty male of this family with an unrelated hyperuricemic female, 4 gouty children resulted. Three of them were also hypertensive and 2 had renal impairment.

Beckett and Lewis found that uric acid levels are low in diabetics and gout rare. They determined serum uric acid levels in 800 diabetics and compared the results with "reported figures," that is, "with those found in normal subjects by similar methods." The use of age-, sex-, and race-matched nondiabetic controls whose uric acid level was determined in an identical manner would have been much preferable.

Pund and colleagues described a case of gouty heart. Urate deposits in the mitral valve were apparently responsible for a loud apical murmur. (See Fig. 33

for a comparable case.) There were deposits of urates distributed diffusely through the myocardium.

Turner and her colleagues could find no difference between white persons and Negroes as to the frequency of clinical gout.

737. Hartnup disease. By screening of patients in psychiatric practice, Hersov and Rodnight found one isolated patient and 2 sisters with what they considered to be Hartnup disease. There was normal urinary indoleacetic acid and indoleacetylglutamic acid but raised indican. Aminoaciduria was present, especially glutamine and serine.

Milne and colleagues studied 2 asymptomatic cases of Hartnup disease (from the original family). Their main findings and conclusions were as follows: (1) absorption of L-tryptophan from the intestines is delayed, a large amount reaching the colon with bacterial conversion to indole; (2) after absorption, less L-tryptophan than normal is oxidized to formylkyneurine. More L-tryptophan than normal is converted to indoleacetic acid and indoleacetylglutamine; (3) aminoaciduria in Hartnup disease is constant; (4) after oral DL-tryptophan, less indolic acid is excreted than after an equal dose of the L-amino acid and no indolyl-3-lactic acid; large amounts of tryptophan appear in the feces; (5) there is defective transport of tryptophan across the jejunum and proximal renal tubules and also deficiency of tryptophan pyrrolase or reduced transport of substrate to enzyme; (6) the cerebellar ataxia may be due to intoxication by retained amino acids; alkalinization of the urine to increase indolic acid excretion would be a rational form of therapy.

Shaw and colleagues showed that after sterilization of the bowel with neomycin, administration of L-tryptophan to a patient with Hartnup disease did not produce an increase in urinary output of indole metabolites.

738. Hemochromatosis. MacDonald and Mallory studied a large autopsy series of hemochromatosis and hemosiderosis. They concluded that idiopathic hemochromatosis should not be viewed as an inborn error of iron metabolism. They think that a dietary factor causes the cirrhosis and that the iron accumulation is secondary. Their evidence is not strong, whereas that of Bothwell and colleagues (¶406) and of Debré and co-workers (¶102) clearly supports the genetic hypothesis. On the basis of studies of the nature of the stored iron in in hemochromatosis, Richter concluded that there must be a defect in cellular iron metabolism.

Dillingham described hemochromatosis in 4 siblings of Spanish-American derivation. He made the interesting suggestion that the designation hereditary hemochromatosis (which has a pleasantly alliterative lilt) would serve the useful function to "induce the physician to investigate the relatives of the patient with the so-called 'sporadic' case. This is especially significant now that repeated phlebotomy shows some promise of arresting the disease."

Fienberg has studied perinatal idiopathic hemochromatosis, as he calls giant cell hepatitis, and suggested that it represents an inborn error of metabolism. Two pairs of affected male siblings who died shortly after birth were investigated.

739. Hyperbilirubinemia. Mandema and colleagues studied families affected by the Dubin-Sprinz-Johnson type of hereditary hyperbilirubinemia. Excretion of conjugated sulfobromophthalein sodium into the bile was markedly delayed, and an excess of it appeared in the urine. Berkowitz, Entine, and Chunn described a case in a Negro man.

Willner, Treiber, and Manderson described a case of chronic hyperbilirubinemia which seemed to be different from the Dubin-Sprinz-Johnson variety because liver biopsy was normal and different from the Gilbert variety because there was bile in the urine, elevated direct bilirubin determination, and poor visualization of the gall bladder. This may have been the Rotor type.

Tygstrup described intermittent jaundice first appearing in the first 2 years of life in 2 boys, probably related, from a small community in the Faroe Islands. Liver biopsy and direct cholangiography revealed intrahepatic cholestasis. During episodes of jaundice, occurrence of weight loss, steatorrhea, elevated serum transaminase levels, and hypopotassemia suggested that the disorder is of more grave import than the Gilbert-Meulengracht syndrome (as the Danish author chooses to call it) or the Dubin-Sprinz-Johnson syndrome.

Haverback and Wirtschafter described a family with the form of familial nonhemolytic jaundice described by Roter (1948) and by Schiff and colleagues (¶397). The presence of both conjugated and unconjugated bilirubin in both the serum and bile distinguishes it from Gilbert's disease. The absence of coarse, brown-staining, lipofuscin-like pigment in the liver cells and the normal results of oral cholecystography make the distinction from the Dubin-Sprinz-Johnson type of hereditary hyperbilirubinemia.

Peck, Rey, and Snell described the occurrence of jaundice with free and conjugated bilirubin in the serum and without liver pigmentation in members of five generations of a family in Turkey. There was a high degree of consanguinity in the family. It is likely that the inheritance is autosomal recessive with quasi-dominant inheritance (¶394) resulting from repeated mating of affected homozygotes with heterozygous carriers. Red cell survival was investigated using Cr^{51}.

740. Hyperlipidemias. Havel and Gordon studied 3 Negro brothers with idiopathic hyperlipemia and demonstrated a defect of lipoprotein lipase. In 2 unrelated males with idiopathic hyperlipemia, the defect was clearly different. The hyperlipemic brothers showed no xanthomata. All 3 had had pretibial ulcers from an early age. All 3 had sickle trait. Although hyperlipemia and sickle trait are not individually accompanied by pretibial ulcers in children, the authors suggested that the combination of the two was responsible for the ulcers. Among others discussing this subject were Constantinides and colleagues, Carlson and Sterner, and Fleischmajor.

741. Hypoglycemia. In 1956 Cochrane and his colleagues observed (J. Clin. Invest. 35:411) that hypoglycemic infants who were fed a high protein, high carbohydrate diet experienced an *increase* in convulsions. Leucine was found to be an amino acid specifically capable of causing hypoglycemia. Mild to moderate depression of blood glucose occurred in one parent when leucine was given,

and these individuals gave histories suggestive of hypoglycemic episodes in youth. Leucine is metabolized first to alphaketoisocaproic acid; this substance also has hypoglycemic effects. In a careful review, Cochrane was forced to conclude that the mechanism of the hypoglycemia is unknown. ACTH and high carbohydrate diet are recommended. Even with treatment beginning at the age of 6 months, prognosis for normal mentality is not good.

Mabry, DiGeorge, and Auerbach described 2 leucine-sensitive children on one of whom family studies were done. The mother was prediabetic, but the father showed leucine sensitivity. Both siblings were normal. In Cochrane's original report, the 27-year-old father of 2 affected children was leucine sensitive (he had a diagnosis of narcolepsy in childhood). DiGeorge and Auerbach reviewed leucine-induced hypoglycemia. Family studies are limited in number. One parent of the reactor child has been a reactor in most instances. The limits of normal in adults should be determined and a systematic family study performed.

Grumbach and Kaplan interpreted their findings in the leucine-sensitive type of idiopathic hypoglycemia to indicate that leucine, isoleucine, and their keto acid analogue induce an increase in the concentration of plasma insulin, irrespective of blood glucose level.

Fajans and colleagues and Marrack, Marks, and Rose produced evidence that L-leucine also induces hypoglycemia (through increased release of insulin) in cases of islet cell tumor. Leucine sensitivity by no means excludes the possibility of islet cell tumor in patients of any age. The presence of a positive family history favors idiopathic hypoglycemia.

Butterfield and colleagues presented evidence to support the view that the hypoglycemic effect of leucine and isovaleric acid in genetically predisposed persons is due to a transient rise in the plasma insulin activities. Assays of plasma insulin were performed. DiGeorge, Auerbach, and Mabry found increase in plasma insulin in one patient but not in a second.

742. Hypophosphatasia. Nakai, Landing, and Petit suggested that histochemical staining of biopsy specimens of skin is an effective method for the diagnosis of hypophosphatasia in cases with borderline levels of serum enzyme. Rosenthal and colleagues studied tissue alkaline phosphatase in this disorder.

Bethune and Dent described 2 sisters, ages 41 and 42, with hypophosphatasia. This disease had not been previously recognized in adults, although it is clear that affected children survive to adulthood. Both sisters had been thought to have rickets in childhood. Both were short (57 7/8 and 57 1/2 inches) and had a deformed sternum, Harrison's sulci, and expanded chondral ends of the ribs. Both had consistently low serum alkaline phosphatase levels and both elevated phosphoethanolamine in the urine. One was asymptomatic. The other was crippled by multiple fractures and painful bones.

Beisel and colleagues described hypophosphatasia in a 36-year-old Air Force sergeant who suffered an incomplete femoral fracture after minimal trauma. The diagnosis was based on consistently low serum alkaline phosphatase values, apparent absence of alkaline phosphatase in the leukocytes, and abnormally high urinary excretion of phosphoethanolamine.

Jelke described a case of hypophosphatasia in an infant. He emphasized the importance of differentiation from vitamin D–resistant rickets (or from ordinary rickets) because high doses of vitamin D are detrimental. The patients tend to have elevated serum calcium levels, probably because of failure of deposition in the bones with normal absorption. Azotemia accompanied the hypercalcemia. Spontaneous remission with healing of the bone lesions started at 7 months in this patient. However, craniostenosis developed, requiring craniotomy at 21 months.

743. Hypophosphatemia. In addition to the more usual sex-linked dominant form, Winters and Graham suggested the existence of a genetic form of hypophosphatemic rickets which is inherited as an autosomal dominant trait. The finding of male to male transmission supported the latter hypothesis. In a companion article, Winters, McFalls, and Graham described a sporadic case in a 7-year-old girl. Suggested possibilities included homozygosity for an unrecognized autosomal recessive trait, a new dominant mutation (either sex linked or autosomal), and phenocopy. The normal range of serum inorganic phosphorus and use of its determination in the diagnosis of hypophosphatemic rickets were studied by Greenberg, Winters, and Graham.

In vitamin D–resistant rickets, Field and Reiss found that infusion of calcium consistently increased the low tubular reabsorption of phosphate to nearly normal levels with increase in serum phosphorus. They suggested that "secondary hyperparathyroidism, presumably due to defective gastrointestinal absorption of calcium, accounts at least in part for the phosphaturia and the hypophosphatemia characteristic of the disease."

744. Lactose disease. Holzel, Schwarz, and Sutcliffe recognized a previously undescribed disease consisting of an inability to hydrolyze lactose. The manifestations were failure to gain weight despite adequate food intake, mild diarrhea, flatulence, and colic. Unsplit lactose apparently gives rise to abnormal fermentation in the intestine with increased fluid excretion and diarrhea. The diagnosis is made by a comparison between the oral lactose tolerance test and the oral glucose and galactose tolerance test. The treatment is the use of nonlactose carbohydrate in the diet. The authors observed the disease in 2 siblings. Manifestations are more likely in breast-fed infants than in infants receiving formulas containing sucrose or glucose. Weijers and colleagues observed the same syndrome caused by invertase and/or maltase deficiency. If the lactic acid content of the feces exceeds one Gm. in a period of 48 hours, the possibility that an alimentary carbohydrate-splitting defect may be interfering should be considered.

Darling, Mortensen, and Søndergaard described lactosuria and aminoaciduria with death in the first weeks of life. They suggested that this is a new inborn error of metabolism, specifically a genetic defect in lactase.

745. Maple syrup urine disease. Otherwise known as branched-chain ketoaciduria, this was discussed by Dancis, Levitz and Westall.

746. Methemoglobinemia (see also ¶802). Scott took advantage of the relatively high frequency of hereditary methemoglobinemia in Alaskan Eskimos and Indians to determine the level of DPN diaphorase in heterozygotes. Diphosphopyridine nucleotide diaphorase activity is lacking in the red cells of persons with the disease, which behaves as an autosomal recessive trait. The enzyme activity is about one-half normal in presumed heterozygotes, e.g., the parents of affected persons.

747. Oroticaciduria. In a single patient, Huguley and colleagues described a metabolic disorder which may be hereditary inasmuch as the one reported case was in the offspring of a marriage between first cousins once removed. The child developed a severe anemia at the age of 5 months characterized by hypochromic red cells and megaloblastic marrow. The urine was found to contain large amounts of crystals which proved to be orotic acid. Iron, pyridoxine, vitamin B_{12}, folic acid, and ascorbic acid were of no benefit. Adrenocorticoids effected some improvement. Almost complete clearing of signs of illness occurred when a mixture of uridylic and cytidylic acids was given. The disorder is thought to represent a genetically determined disorder of pyrimidine metabolism. Uridylic and cytidylic acids are constructed from orotic acid via orotidylic acid. The enzyme defect apparently involves this formation. In addition, a feedback influence of cytidylic acid on the steps leading up to orotic acid is thought to be lacking in oroticaciduria.

748. Oxaluria and oxalosis. Hall, Scowen, and Watts reviewed the clinical features of primary hyperoxaluria, on the basis of 8 cases in three families. In one family, the parents were first cousins. Autosomal recessive inheritance is suggested. No method for preventing the formation of calculi and of extrarenal deposits is known. Death in uremia is invariable.

Shepard and colleagues found hyperoxaluria in 5 individuals of three successive generations of a nonconsanguineous family. Renal calculus had occurred only in the proband. Dominant inheritance was proposed. The proband died of renal failure at the age of 7 years. Many tissues in addition to the kidneys revealed exalate deposits.

Stauffer reported on a Negro girl dying of oxalosis at the age of 13 years. Neither parent had hyperoxaluria. Daniels and colleagues studied 3 affected siblings.

749. Pentosuria. Hiatt, Freedberg, and Feingold succeeded in identifying heterozygous carriers of pentosuria by administration of glucuronolactone, an L-xylulose precursor. Heterozygous individuals had a serum level of L-xylulose and a urine pentose level intermediate between the levels in normal and in pentosuric persons.

Roberts described a mother and her son and daughter with pentosuria (xyloketosuria). The family was Jewish, derived from Poland and Russia where there are known to be population groups with high gene frequencies for pentosuria. Roberts referred to two other reports of pentosuria in successive gener-

ations. All these instances may not be exceptions to the usual autosomal recessive inheritance but rather instances, like that in alkaptonuria (¶730), of a quasi-dominant pattern of inheritance resulting from inbreeding.

Touster discussed the stimulation of L-xylulose excretion, which is produced in pentosuric persons by certain drugs such as aminopyrine, antipyrine, chloreton, and barbital. Pentosuria is a disorder of no apparent pathologic significance, and the exaggeration of the pentosuria by drugs is probably similarly benign.

Iuchi and Shibata described a paper electrophoresis method for identification of sugars and other reducing substances in urine. Glucose, fructose, ribose, rhamnose, lactose, maltose, sucrose, glucuronic acid, and glucosamine are easily identified by this technique.

750. Phenylketonuria (Garfield and Carver). Meulemans discussed the quantitative and qualitative ferric chloride test for phenylpyruvic acid in urine. Bessman and Tada studied indicanuria in phenylketonuria and interpreted their results as indicative of a generalized derangement of the metabolism of indole compounds secondary to phenylalanine excess. A phenylalanine block of tryptophan metabolism was suggested as the mechanism of the mental deficiency in phenylketonuria, and indicanuria was proposed as a better and simpler way to judge the efficacy of a low phenylalanine diet than blood phenylalanine level.

Waisman and colleagues observed that the characteristic abberations of human phenylketonuria, namely, high plasma phenylalanine, phenylketonuria and characteristic odor, occur in adolescent monkeys fed excessive amounts of L-phenylalanine. Retardation in learning ability resulted. Four infant macaques were separated from their mothers at birth and given a high phenylalanine diet. Evidence of mental retardation in these animals and typical grand mal seizures in two were observed. Studies of intermediary metabolism in these animals may shed light on the mechanisms of the disease in man.

Screening techniques for early detection of phenylketonuria were discussed by Centerwall, Chinnock, and Pusavat and by Allen.

Jervis detected heterozygotes by determining the time course of tyrosine blood levels after giving 2 mM. L-pnenylalanine per kilogram by mouth. The heterozygous carriers showed curves intermediate between the steep curve of the normal and the flat curve of the affected homozygotes.

Fleisher and Zeligman found that all 23 patients studied had fair skin and light hair and 19 of them had blue eyes.

Sutherland, Berry, and Shirkey described an 8-year-old phenylketonuric child with normal intelligence and another 3 years 7 months old with near normal intelligence. The manifestations were largely behavioral and were improved by a phenylalanine-restricted diet. The clinical aspects were (1) dull, expressionless face, (2) negativistic behavior, (3) apprehensiveness, (4) emotional outbursts, and (5) speech disturbance.

Renwick, Lawler, and Cowie and Hsia and Steinberg studied linkage in phenylketonuria but could demonstrate none with the markers, mainly blood groups, used.

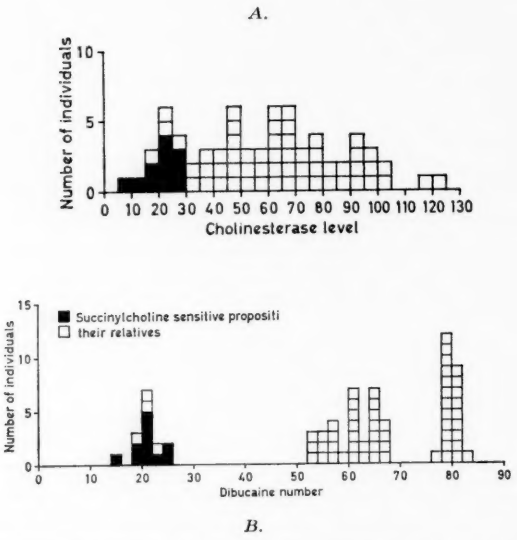


Fig. 34.—Determination of pseudocholinesterase phenotype. *A*, When cholinesterase is measured using acetylcholine as the substrate, the individuals with suxamethonium sensitivity (in black) fall at the lower end of a continuous distribution. *B*, When benzoylcholine is used as the substrate and when the percentage inhibition of the hydrolysis of this substrate by dibucaine (the "dibucaine number") is studied, three sharply separate phenotypes are discovered. (From Harris, H., Whittaker, M., Lehmann, H., and Silk, E.: Acta genet. 10:1, 1960.)

Moncrieff and Wilkinson were unable to confirm the benefit of fructose treatment in phenylketonuria which had previously been claimed. Dietary management was discussed by Lyman and Lyman and by Acousta and Centerwall among others.

751. Porphyria. Waldenström and Haeger reported studies of porphyria cutanea tarda, which seems to be chemically distinct from congenital or erythropoietic porphyria and from acute intermittent porphyria. (A fourth type of porphyria is that of southern Africa studied by Dean and Barnes.) However, porphyria cutanea tarda may have in part a genetic background, since Haeger found evidences of deranged porphyrin metabolism in seemingly normal relatives. Alcohol has been incriminated as a precipitating factor and a parallel drawn to primaquine sensitivity and succinylcholine sensitivity. Barbiturates are precipitating agents in acute intermittent porphyria. Watson reviewed the subject in detail.

Schmid described the cutaneous porphyria which has occurred in almost epidemic proportions in the summer months of recent years in Turkey. Both Turkish and Kurdish people have been affected. Rural dwellers have been affected more than urban. The suggested cause is the fungicide hexachlorobenzene added to seed wheat. High quality seed treated with fungicide is distributed annually to the farmers. It is clear that some of the wheat was used for human consumption rather than planting. The human consumption was not limited to rural areas; some of the treated wheat is thought to have reached urban markets.

"If this can be established beyond doubt, it would probably represent the first direct evidence for the occurrence of an acquired toxic form of porphyria in man." Cetingil and Özen gave a detailed account of the condition.

Eilenberg and Scobie described prolonged neuropsychiatric disability with acute intermittent porphyria, a feature which is relatively familiar, and electrocardiographic changes they interpreted as indicative of porphyric cardiomyopathy. They referred to the findings by others of "marked disintegration of myocardial fibers."

752. Pseudocholinesterase, defect in. Harris and colleagues studied families of 11 persons sensitive to suxamethonium (succinylcholine). The frequency curve for pseudocholinesterase levels is continuous when acetylcholine is used as the substrate (Fig. 34*A*). The sensitive persons all fall at the lower end of the bell-shaped curve. However, on this evidence alone, a polygenic mechanism might be suggested. In terms of dibucaine number, however, three distinct groups are identified (Fig. 34*B*). (The dibucaine number is the percentage inhibition of benzoylcholine hydrolysis by dibucaine.) The three phenotypes are thought to correspond to the three genotypes resulting from a two allele system.

Lehmann and colleagues described what may be a new pseudocholinesterase phenotype. A father and 5 children had abnormal serum pseudocholinesterase levels. The mother and one child were normal. The father and 5 children showed dibucaine numbers in the range between those of the intermediate and atypical phenotypes of earlier studies. However, the esterase activity was grossly depressed in the 5 children and moderately depressed in the father. The authors suggested that the abnormal individuals represented a new phenotype determined by a rare abnormal gene for which they are heterozygous.

In pigs, Augustinsson and Olsson studied acetylarylesterase, which, like cholinesterase, catalyzes the hydrolysis of aromatic esters. Considerable individual variation, with values ranging from zero to 200, was observed. Family data suggested to the workers the presence of multiple allelic genes with additive effects. The notation used and the enzyme activity resulting from each allele were:

ALLELIC GENE	ENZYME ACTIVITY
a	0
A1	25
A2	50
A3	75
A4	100

The various genotypes appeared to display additive effects of the alleles as illustrated here:

GENOTYPE	PHENOTYPE
aa	0
aA2	50
A1A1	50
A1A3	100
A3A4	175

The segregation observed in various matings supported the hypothesis of multiple additive alleles, for example:

♀ 75 aA3 × ♂ 25 aA1

1 ♀ 2 ♂	1 ♂	2 ♀ 2 ♂	2 ♀ 1 ♂
aa	aA1	aA3	A1A3
0	25	75	100

The authors suggested that the A2, A3, and A4 alleles may be duplicate, triplicate, and quadruplicate forms of the A1 allele.

753. Sucrosuria. Moncrieff reported further cases in which abnormal amounts of sucrose are passed in the urine.

754. Wilson's disease (Forssman). Bearn published a genetic analysis of thirty families with 32 patients affected by Wilson's disease. Seventy-nine per cent of the patients came from two circumscribed areas: 44 per cent were from eastern Europe (Jews) and 25 per cent came from the Mediterranean (non-Jews). The Jews tended to have later onset of the disease and showed greater variance in the serum copper and ceruloplasmin levels, as compared to the Mediterranean group. The patients with a normal level of ceruloplasmin came from the eastern Jewish group. Explanations such as genetic modifiers or different alleles were discussed.

Sherwin, Beck, and McKenna described a 23-year-old woman with Wilson's disease who experienced a remission beginning in the first trimester of pregnancy and persisting for at least 6 months after delivery of an apparently normal infant. Ceruloplasmin did not rise. Improvement was thought due to transfer of copper from the mother to the fetus.

Anderson and Popper analyzed the hepatic histopathologic state in 20 cases of Wilson's disease. The cirrhosis was classified by them as postnecrotic. Unusual features included the finding of excessively large Kupffer cells and liver cell nuclei ballooned by large amounts of glycogen. Extensive fatty metamorphosis of liver cells occurred in some. Liver biopsy in an asymptomatic sibling of a patient with Wilson's disease (serum ceruloplasmin was absent in the sibling) revealed large glycogen-stuffed liver cell nuclei.

Gilsanz, Barrera, and Anaya performed sixteen renal biopsies in 5 patients with Wilson's disease and could demonstrate no abnormality and no change.

Richterich and colleagues could separate ceruloplasmin into two fractions with polyphenyloxidase activity. The first, which they call C-C, represented about 75 per cent of the total ceruloplasmin and the second, which they called C-D, about 25 per cent. C-C was lacking or deficient in Wilson's disease, and C-D was high relative to the total. Newborn children and nephrotic individuals have levels of C-D higher than C-C. These workers suggested that C-D is a precursor of C-C and the enzymatic mechanism for the change of C-D to C-C is lacking in Wilson's disease.

Litin and Goldstein discussed the use of penicillamine in Wilson's disease, pointing out that it has a more potent cupruric effect than BAL and has the additional advantage of oral administration. Scheinberg and Sternlieb view Wilson's disease as due to a combination of the hereditary inability to synthesize normal amounts of ceruloplasmin and an environmental factor, copper. Treatment directed at the environmental factor in 10 patients was described: low copper diet, potassium sulfide, penicillamine, and BAL. Although the neurologic manifestations are ameliorated, the patients often die of liver failure despite treatment. Earlier treatment is probably the answer.

755. Miscellaneous. Knapp described a disturbance, probably of genetic basis, involving tryptophan metabolism in successive generations of three families. Dominant inheritance was suggested. After administration of tryptophan urinary excretion of kynurenine, oxykynurenine, and xanthurenic acid increased ten to twenty fold in affected persons. The disturbance would be temporarily eliminated by administration of vitamin B_6. Clinically, the families showed the following disorders (in order of frequency): bronchial asthma, chronic urticaria, anemia, diabetes, varices, and leg ulcers. A relationship to the disturbance in tryptophan metabolism is speculative.

Coles, Priestman, and Wilkinson found a 4-year-old child who excreted a previously undescribed substance in the urine. The child was mentally and physically retarded. The material, called T substance by the authors from the initial of the child's surname, is apparently an abnormal product of purine metabolism, chemically similar but not identical to alloxan.

In 14 of 1,276 newborn infants, Bloxam and colleagues found large amounts of *p*-hydroxyphenylpyruvic acid, *p*-hydroxyphenyllactic acid, and tyrosine. It occurred with normal diet supplemented by ascorbic acid, in apparently healthy infants without hepatic dysfunction, and in both full-term infants and premature infants. It was observed to an age as late as 68 days. The abnormal excretion ceased without treatment. The authors suggested that the findings were explained by a lack of an enzyme which catalyzes the conversion of *p*-hydroxyphenylpyruvic acid to homogentisic acid and that the enzyme has a variable age of appearance.

Menano and colleagues described what appears to be an inborn error of metabolism and is manifested by cheilosis-like lesions of mucous membrane and skin, seborrheic dermatitis, and aminoaciduria. Glutamic acid and glycine were found in the urine in excess. Administration of pantothenic acid modified the aminoaciduria and symptoms to some extent.

Rosenberg, Watkin, and Mueller studied the inborn error of metabolism which was first described by Rowley and colleagues and which is characterized by aminoaciduria, dwarfism, and weakness.

VIII. CONGENITAL MALFORMATIONS

756. Symposium. Wolstenholme, G. E. W., and O'Connor, C. M.: Ciba Foundation Symposium on Congenital Malformations, London, Jan. 19 to 21, 1960, Boston, 1960, Little, Brown & Company.

Chromosomal (Ford) and genetic (Penrose) mechanisms were discussed as well as environmental factors (Ingalls) and experimental teratogenesis (Murphy, Tuchmann-Duplessis, and Mercier-Parot; others). McKeown and Record analyzed the frequency of malformations in a population observed for 5 years after birth. Of interest is their Fig. 2 (p. 13) showing that the proportion of patients with cardiac malformation who were twins was in excess of the proportion of multiple births in the total population. The difference did not quite attain significance at the 5 per cent level. The finding is of interest as an indicator of one possible factor in the low concordance rate for congenital heart disease shown by monozygotic twins.

Penrose (p. 23) referred to the evidence of Polman (Genetica 29:29, 1951) on the genetic factor in congenital heart disease in association with anencephaly. Edwards (p. 30) indicated that there is a sex-linked recessive variety of hydrocephalus. Aqueductal stenosis appears to be the responsible lesion.

Penrose (p. 48) raised the question of whether the chromosomes with satellites or the nucleoli (in the formation of which the chromosomes with satellites are concerned) are sticky so that there is increased risk of their participation in translocations. Ford thought this possible. In fact, his Fig. 1 (p. 35) shows two probably nonhomologous chromosomes "attached" end to end at the satellites.

Ingalls reviewed findings from the literature purporting to implicate certain environmental factors in teratogenesis in man. Ingalls and Davies (1947) reported 7 cases of Mongolism, 6 of which had been preceded by maternal infections in the second or third month of gestation. Loeb (1949) found one Mongoloid offspring in 11 born of mothers with influenza A at or near the end of the second month of pregnancy. Coffey and Jessop (1959) found Mongolism in the offspring of women who had Asian influenza in pregnancy. Ingalls comments further, "There was a very impressive case, taken from the French literature, of a young unmarried mother who attempted suicide [with carbon monoxide] at about the eighth week, and she had a mongoloid child." All this was one year after the discovery of the chromosomal basis of Mongolism was announced!

The relationship of hypothyroidism and prediabetes (Hoet) and of hydramnios (Stevenson) to congenital malformations was discussed. The teratogenic effects of various tumor-inhibiting chemicals (Murphy; Tuchmann-Duplessis and colleagues) were also covered. Actinomycin D, an antibiotic which also has antimitotic effects, is of interest because it is teratogenic in exceedingly low concentration.

757. Beginning in January, 1960, The National Foundation published an annotated review of current literature on congenital anomalies. General discussions were given by Wilson, among others.

758. Nishimura and Nakai found malformations, mainly skeletal, in the offspring of female mice given caffeine in pregnancy. Certain parallelism exists between the mutagenic, carcinogenic, carcinostatic, and teratologic effects of chemical agents. The mutagenic effects of caffeine are discussed elsewhere (¶345).

759. Schaefer found a high frequency of abnormal placentation and fetal malformations in certain family groups of Baffin Island Eskimos in the Canadian Arctic. A relationship between the two observations was suggested.

760. Frazier analyzed data on congenital malformations from birth certificates in Baltimore (Table XV). Polydactyly is much more frequent in Negroes than in Caucasians. Excluding polydactyly, congenital malformations are more frequent in white persons. Because of the high rate for polydactyly, total congenital malformations are more frequent in Negroes. That less astute observation by those examining Negro infants was not responsible is indicated by the finding of identical results in the Johns Hopkins Hospital, where the observations on Caucasians and Negroes were made by the same persons.

De Rudder claims that the frequency of congenital malformations has increased markedly in the last 30 years. The frequency of congenital heart disease and of congenital spinal malformations, including meningocele, myelocele, and meningomyelocele, was studied in the Frankfort (Germany) University Hospital. Between 1951 and 1958, the frequency of spinal malformations was 6.41 per 1,000 infants admitted and 2.56 per 1,000 total admissions. In the period from 1936 to 1939, the corresponding figures were 1.87 and 0.39.

TABLE XV

	RATE PER 1,000 LIVE BIRTHS		
	TOTAL	WHITE	NONWHITE
Polydactyly	1.7	0.3	3.6
Malformations other than polydactyly		6.5	4.3
All malformations		6.8	7.9

761. Fraser reviewed causes of cleft palate and lip. He referred to his discovery of the teratogenic effects of cortisone in 1950, the fact that the dose of cortisone and the stage of gestation are important factors, the observation that 100 per cent of one mouse strain and only 17 per cent of another developed cleft palate with the same conditions, the correlation of the latter observation with the finding that the "cortisone-resistant" strain of mouse had an earlier onset of palatal closure, and the finding that puncture of the amniotic sac may result in cleft palate possibly through shift in critical pressure relations. The relevance of experimental studies to the human malformation is difficult to determine. Since about 60 per cent of one egg twins are discordant for cleft lip, it would seem that the environmental differences may be rather subtle. "Searches for prenatal environmental teratogens in humans are likely to be unrewarding and the greatest progress may come from studies of the embryos themselves to find out, in biochemical terms, what the genes are doing to make them so sensitive to their environment."

Trasler found that within the A/Jax strain of mice, embryos in the uterine site nearest the ovary develop cleft lip, with or without cleft palate, significantly more often than embryos in other positions in the uterus. Wheat observed hairlip in Shorthorn cattle.

Fig. 35.—Apert's acrocephalosyndactyly.

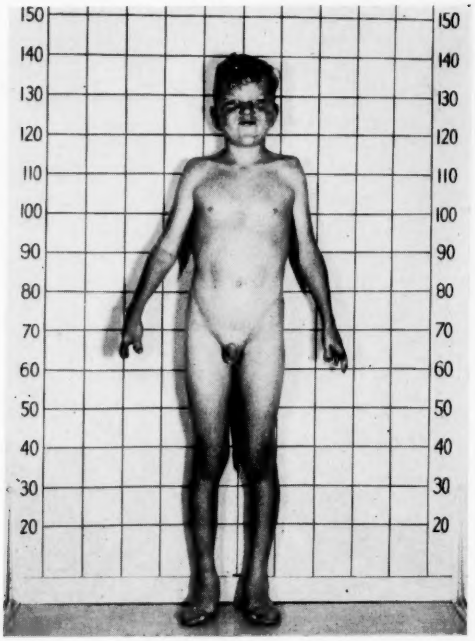


Fig. 35*A*.—K. K. (457071), a 12-year-old white boy, had an IQ of about 67. The cervical spine shows characteristics of the Klippel-Feil syndrome (block vertebra of C2 and C3; fusion of neural arches and spinous processes of C5 and C6). At the time of the proband's birth, the father was 52 and the mother 21 years old. The parents are not related. One older and 4 other younger children are unaffected.

B. *C.*

Fig. 35*B* and 35*C*.—Typical changes of the extremities.

762. Stallybrass described anencephaly in one of uniovular (monochorionic) twins. Furthermore, Lewis found anencephaly in both of dizygotic twins.

D. *E.*

F.

Figs. 35*D*, 35*E*, and 35*F*.—Roentgenologic views of the skull and extremities.

763. Blank assembled case material on 54 patients with *acrocephalosyndactyly* (Fig. 35) born in Great Britain. Two clinical categories were clearly distinguished: (1) "typical" acrocephalosyndactyly, to which Apert's name is appropriately applied, and (2) other forms, lumped together as "atypical" acrocephalosyndactyly. The feature distinguishing the two types is a middigital hand mass with a single nail common to the second, third, and fourth digits, present in Apert's syndrome and lacking in the others. Thirty-nine of the 54 cases were of the Apert variety.

Fig. 36.—Treacher Collins syndrome. In 1949 the monograph of Franceschetti and Klein (Acta ophth. 27:143) appeared describing the mandibulofacial syndrome. (1) "anti-Mongoloid" obliquity of the palpebral fissures, (2) coloboma most often in the outer portion of the lower lids, more rarely in the upper lids, (3) hypoplasia of the malar bones and mandible, (4) deformed external ear and sometimes middle and inner ear, (5) large mouth with irregular teeth and malocclusion, and (6) blind fistula and/or skin tags on a line between the mouth and ears. In 1900 Treacher Collins wrote about the same disorder.

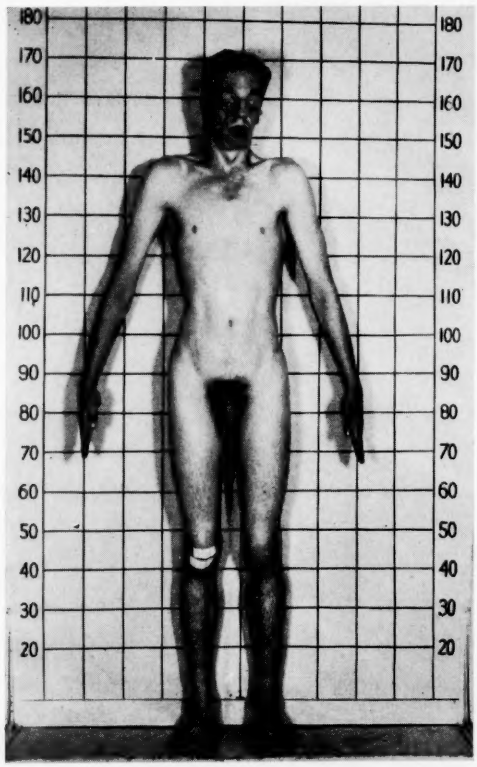


Fig. 36*A*.—W. E. H. (161141), 22 years old, shows the characteristic features outlined above. By x-ray, no mastoid air cells are demonstrable. Except for the changes in the skull, no other skeletal anomalies are demonstrable.

Postmortem data were available on 12 patients. Six had visceral anomalies. However, in no 2 were identical visceral malformations found, and no evident pattern to the malformations was observed.

A survey of obstetric records suggested a frequency of Apert's syndrome at birth of about one in 160,000. The number of living patients gave an estimate of one in 2,000,000 for the frequency of the condition in the general population.

The frequency of Apert's syndrome showed no correlation with birth order. There was, however, increased average parental age. Paternal age could be shown to be the main factor.

The low frequency of consanguineous matings and the failure to observe multiple affected siblings are evidence against simple autosomal recessive inheritance. None of Blank's patients had married. The only parent-child combi-

nations known are (1) the one described by Weech (1927) and (2) the one of van den Bosch included as an appendix to Blank's report. All features of the disorder seem consistent with the view that the overwhelming majority of cases of Apert's syndrome represent new dominant mutations.

Males and females are affected in equal proportions.

Chromosome analysis in one case showed no abnormality.

Atypical acrocephalosyndactyly is probably etiologically distinct from Apert's syndrome. In seven well-authenticated families, multiple siblings have been affected by the atypical form. Apert's syndrome and the atypical form have never been found together in the same family.

A mutation rate of 3×10^{-6} per gene per generation was estimated, a figure in agreement with estimates on other dominant traits. The mutation rate appears to be five times as great in a father age 37 as in a father age 27.

Finally, the author compared the difference between mean maternal and paternal age in Apert's syndrome (+5.1) with that in achondroplasia (+5.7; average of three studies) and that in the Marfan syndrome (+8; Lynas, 1958).

764. Monnet and colleagues and Stovin, Lyon, and Clemmens described cases of *mandibulofacial dysostosis* or Franceschetti's syndrome. Treacher Collins' name is also attached to the condition. (See Figs. 36 and 37.)

Peters and Hövels discussed *maxillofacial dysostosis.*

In 2 sisters, Gorlin, Chaudhry, and Moss described what is probably a new syndrome. The features were craniofacial dysostosis, hypertrichosis, hypoplasia of the labia majora, dental and eye anomalies, and patent ductus arteriosus. The sisters were of average, or better than average, intelligence.

B. *C.*

Fig. 36*B* and 36*C*.—He has no external auditory canals, and any hearing loss present seems to be conductive in type; hearing by bone conduction is very good. Although he is institutionalized with mentally defective persons, it is considered possible that he is, in fact, of average intelligence, with limited opportunity to learn.

A. *B.*

Fig. 37.—Treacher Collins syndrome. *A* and *B*, M. H. (773393), 18 years old, has micrognathia, coloboma of the right upper lid, and bilateral accessory auricular appendages. The external ear and external auditory canal are totally absent on the right. The zygomatic arch is hypoplastic, which results in absence of the normal malar eminences.

765. Gabr and colleagues provided the autopsy findings in a 9-year-old girl with *progeria*. Changes in the epiphyses were interpreted as indicating reduction in the formation of enchondral bone. The clavicles were completely replaced by fibrous tissue. Most interesting is the fact that a sister, still living, has progeria; the parents are first cousins. To our knowledge, multiple cases of progeria have not previously been described, neither has there been comment on parental consanguinity.

Macdonald, Fitch, and Lewis described the *Cockayne syndrome* in 3 of 5 siblings. The features resemble progeria in some respects, but it appears to be a distinct entity. Characteristics are dwarfism, precociously senile appearance, pigmentary retinal degeneration, optic atrophy, deafness, marble epiphyses in some of the digits, sensitivity to sunlight, and mental retardation. Mental retardation, skin hypersensitivity, retinal degeneration, and normal blood lipid levels serve to distinguish Cockayne's syndrome from Gilford's progeria. Presumably the inheritance is autosomal recessive.

Seckel reported in a monograph his studies of "*bird-headed dwarfs.*" This designation and that of nanocephaly were assigned by Virchow. In addition to extreme dwarfism, the features are small head, large eyes, beaklike protrusion of the nose, narrow face, and receding lower jaw. Mental retardation, in spite of the spectacular smallness of the brain, is not as marked as in microcephaly. Congenital malformations such as pancytopenia and osseous deformities occur. Seckel's comments are based on 2 cases he observed in Chicago and on 13 reliable and 11 less reliable cases from the literature. Multiple occurrence in the same sibship, increased parental consanguinity, occurrence in both sexes, and the normality of the parents suggest autosomal recessive inheritance.

IX. ALIMENTARY TRACT, INCLUDING PANCREAS, BILIARY TRACT, AND LIVER

766. General discussions were given by McConnell and by McKusick. Buckwalter, Scoy, and Knowler studied ABO blood groups in sibships containing one or more members with *peptic ulcer.* As in the earlier study of Clarke and colleagues in Liverpool, the results were in the direction of supporting a causal nature of the O-nuclear association (p value between 0.05 and 0.10).

767. The Zollinger-Ellison syndrome. Gregory and colleagues succeeded in extracting, from the pancreatic tumor of a patient with Zollinger-Ellison syndrome, a substance with the chemical and physiologic properties of the antral hormone gastrin. The material stimulated gastric secretion of acid but not of pepsin. They could demonstrate that insulin or histamine was not responsible for the effects. Osborne, Brown, and LeCompte also extracted a gastrin secretagogue from an ulcerogenic nonbeta cell pancreatic islet tumor which was malignant. The characteristics of the substance they found were essentially the same as those of the substance described by Gregory and colleagues.

Loughridge, Neill, and Willis, Felts and colleagues, and Dijk, among others, described cases of the Zollinger-Ellison syndrome. Chvojka had a female Negro patient. Zollinger, Gray, Roth, Spiro, and others participated in a symposium on the relationship between endocrine hyperfunction (pancreatic, adrenal, parathyroid, pituitary) and peptic ulcer.

Rawson and her colleagues described a 55-year-old man with an 8 year history of intractable diarrhea and a 2 year history of symptoms of peptic ulcer. Investigations showed gross gastric hypersecretion and steatorrhea. Resection of the pancreatic tumor alone cured the diarrhea and ulcer symptoms and resulted in a decrease in acid secretion. In previously reported cases, gastric resection was performed as well as resection of the pancreatic tumor. The experience of Rawson and colleagues represents proof of the causal relationship of the pancreatic adenoma to the syndrome. In connection with the mechanism of the diarrhea, Rawson pointed out the difficulties such patients have in maintaining alkaline duodenal contents because of the gastric hypersecretion. In an acid milieu, lipase and other small intestine enzymes may be inactivated or even destroyed. Others have indicated diarrhea, often with pronounced loss of electrolyte, as a manifestation of the Zollinger-Ellison syndrome. In fact, marked and obscure potassium depletion was the presenting feature of the patient reported by Charles and Cochrane.

Small intestine: 768. See ¶744 for the *celiac syndrome* accompanying genetic defects in carbohydrate splitting in the bowel. See ¶725 for the celiac syndrome which accompanies alipoproteinemia and acanthocytosis.

Fone and colleagues, from intestinal biopsy studies correlated with hematologic, radiographic, biochemical, and absorption studies, concluded that adult celiac disease (idiopathic steatorrhea, nontropical sprue) comprises two and possibly more distinct entities. Specifically, there is one seemingly distinct group in which intestinal villi are absent.

Zetterqvist and Hendrix studied the electron microscopic features of the intestinal epithelium in adult celiac disease (nontropical sprue) and concluded that the changes are reversible with a gluten-free diet. Specifically, the brush border was absent before treatment, whereas on gluten withdrawal it reappeared when the evidence of malabsorption disappeared. On the other hand, Rubin and his colleagues, on the basis of ordinary histologic study of 114 biopsies in 32 celiac patients, 7 of whom had been on a gluten-free regimen, concluded that the changes in the bowel are irreversible. (The observations are not inconsistent since different aspects of the anatomic structure of the mucosa were studied.) They concluded that celiac disease and adult nontropical sprue are identical. They described identical biopsies in monozygotic twins with celiac disease and in a mother with nontropical sprue and her daughter with celiac disease.

Wilson and colleagues discussed their studies of intestinal transport of sugars and amino acids, a subject potentially important in many genetic disorders such as Hartnup disease (¶737) and possibly the sugar absorption defects discussed in ¶744.

769. Cases of the *Peutz-Jeghers syndrome* were reported by Bartholomew, Dahlin, and Waugh, by Tucker and Bolande, by Katzen and colleagues, by Allen and Hershey, by Kutscher and colleagues, and by others. Because of the benign nature of the polyps in the Peutz-Jeghers syndrome, systematic removal or fulguration by multiple enterotomy, not bowel resection, is the indicated therapy (Allen and Hershey). Tucker and Bolande's patient had polyps of the duodenum. Mucocutaneous pigmentation apparently identical to that in the Peutz-Jeghers syndrome was described by Bandler in those members of a family affected by extensive hemangiomata of the small intestine from the ligament of Treitz to the ileocecal valve. The bowel lesion was proved in a man and his son and daughter and was probable in another daughter and in a grandson. Appreciation of the fact that the bowel lesion in the Peutz-Jeghers syndrome is hamartomatous results in less surprise that occasionally it is hemangiomatous rather than polypous.

Moskow and Tenen described a 77-year-old man with repeated gastrointestinal bleeding on the basis of intestinal polyposis of the Peutz-Jeghers syndrome. An unusual feature was the onset of symptoms with abdominal pain at the age of 68 years.

Intestinal neurofibromata were described as the cause of gastrointestinal bleeding by Wilson and Anderson.

770. Large intestine. Mayo described a patient with *familial polyposis of the colon* in whom colectomy with preservation of the rectum was performed in 1935. Thereafter, literally hundreds of polyps which developed in the rectum were fulgurated. The patient is living and well at the age of 64 years. A general discussion was given by Veale. Duhamel, Berthon, and Dubarry did a statistical analysis of sixty-seven families (of which eleven were studied personally) affected by multiple polyposis of the colon. The hypothesis of autosomal dominant inheritance was supported. The penetrance of the gene was estimated to be greater than 80 per cent.

Gorlin and Chaudhry described three families with the *Gardner syndrome*:* multiple intestinal polyposis, multiple osteomatosis especially of the mandible and bones of the skull, and sebaceous cysts (¶648). In addition to numerous colonic polyps, a polyp of the "lower one-third" of the duodenum was discovered by upper gastrointestinal series and removed in one patient. There has been only one other report of a small bowel involvement in the polyposis of this syndrome. Several persons in their families were known to have died of adenocarcinoma of the colon. (See Fig. 38.)

Turcot, Després, and St. Pierre described brother and sister with *polyposis of the colon* in association with *tumor of the central nervous system:* medulloblastoma of the spinal cord in one, glioblastoma of the frontal lobe in the other. In the brother, malignant change had taken place in certain of the colonic polyps. This may represent a genetic variety of polyposis distinct from the Peutz-Jeghers syndrome, the Gardner syndrome, and "garden variety" familial polyposis of the colon.

Ecker and colleagues reported a patient with *hereditary hemorrhagic telangiectasia* and massive gastrointestinal bleeding requiring right colectomy. The case is noteworthy for the fact that the site of bleeding was low in the gastrointestinal tract.

Winstone, Henderson, and Brooke found no peculiarity of ABO and Rh blood group frequencies in 277 cases of *ulcerative colitis.* In 163 cases studied, secretor status also showed expected frequencies. Birnbaum, Groen, and Kallner found ulcerative colitis to be much less frequent in Eastern Jews than in Western Jews living in Israel.

Pancreas: 771. Beall and colleagues described fatal *acute hemorrhagic pancreatitis* occurring simultaneously in identical twins age 31 years. Both were chronic alcoholics.

Aird, Lee, and Roberts found a moderately significant excess of group A and deficiency of groups O and B in 620 patients with *cancer of the pancreas,* an insignificant excess of group A in 610 patients with cancer of the esophagus, and no deviation in ABO frequencies in 480 patients with pituitary adenoma.

772. All aspects of current research on *cystic fibrosis of the pancreas* were discussed in a conference held in 1959 and published in 1960 under the editorship of Rustin McIntosh.

Marks and Anderson described cystic fibrosis of the pancreas in a 46-year-old man. The patient was still alive at the time of report. He had always been short of stature and asthmatic. Diarrhea had its onset at 29. He was found to have pancreatic achylia. Sweat chloride determination was 70 mEq. per liter, a value high for children but at the upper limit of normal for adults. The family history was consistent with the diagnosis: in the sibship of the proband and among his first cousins there were, in addition to two stillbirths and an infant who died

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*Gorlin, Chaudhry, and Kelln, claiming credit for a fellow dentist, suggested the eponym Fitzgerald-Gardner. Fitzgerald described the condition in 1943 in the *Journal of the American Dental Association.*

Fig. 38.—The Gardner syndrome. F. M. (783329) and his brother D. M. (469395) have been seen at this hospital for removal of tumors. The mother had numerous "soft tumors" of the head and body and died of carcinoma of the sigmoid colon at the age of 55 years. A sister and brother of the men also have tumors of the face. Three other siblings are apparently normal. No bowel symptoms are present in any of the siblings.

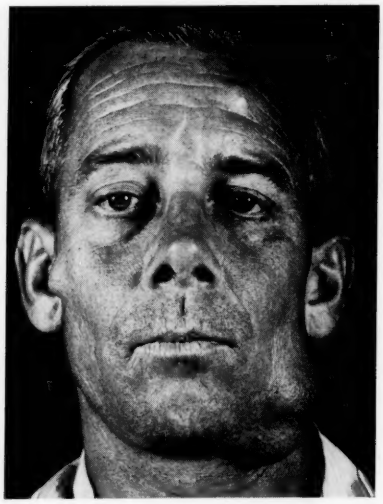
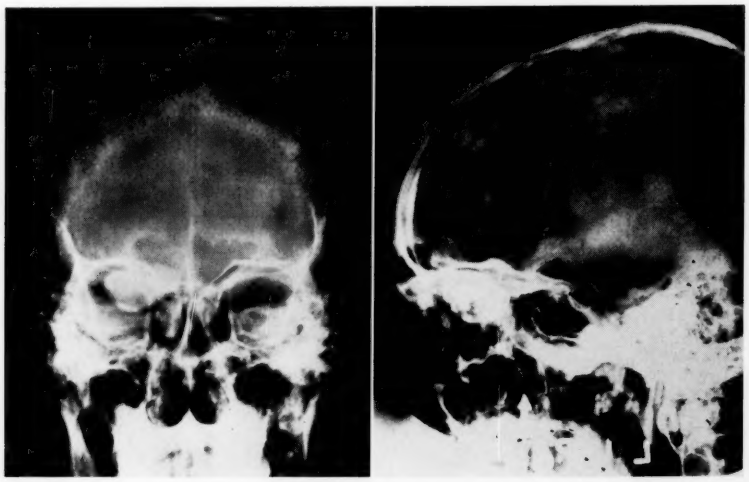


Fig. 38*A*.—At the age of 10 years, F. M. had a tumor removed from the left eyelid. Note that the right eye is more prominent than the left, suggesting encroachment on the orbit by the osteoma shown in *B* and *C*. There is an epithelial cyst on the forehead and right cheek. Although the patient has no bowel symptoms, sigmoidoscopy and barium enema revealed six or more polyps of the colon, and colectomy is contemplated.



B. *C.*

Fig. 38*B* and 38*C*.—Roentgenologic views of osteomas of the orbit and calvarium.

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at 6 months, one who died at 8 months of heat stroke, one who died at 7 years of pneumonia, and one with proved bronchiectasis who died at age 13.

Karlish and Tarnoky maintained that mucoviscidosis is a frequent cause of chronic lung disease in adults. Their evidence consists exclusively of sweat electrolyte studies in the patients of a chest clinic. High sweat chloride is, in our opinion, a doubtful criterion on which alone to base a diagnosis of mucoviscidosis. Much more convincing would be a demonstration of an increased frequency of adults with chronic lung disease in the families of probands with cystic fibrosis; in fact, such was not found by Roberts (see below).

The feasibility of surveying school children with the palm print type of sweat test was demonstrated by Kulczycki, Macleod, and Schwachman.

Steinberg and Brown attempted total ascertainment of cystic fibrosis among white children born alive in Ohio during the years 1950 through 1953. They found the frequency to be one in 3,700, a figure about one-fourth that of previous estimates. Anderson and Hodges (1946) estimated one in 600 and Goodman and Reed (1952) one in 1,000. The estimated frequency of homozygous affected children gives a gene frequency of about 0.016, and about 3 per cent of white persons are heterozygotes. Although the new estimate is lower, cystic fibrosis remains "the most frequent lethal genetic disease among white children."

Bruce, Denning, and Spalter reviewed the ocular findings in 24 patients with cystic fibrosis with moderate to severe lung changes. Venous engorgement, papilledema, hemorrhages, and cystic changes in the region of the macula were noted. Two of 24 had appreciable carbon dioxide retention; 6 of 15 had elevated venous pressure; 3 of 10 had elevated cerebrospinal fluid pressure. Pathogenesis of the ocular changes was not completely certain. However, the similarity in several respects to those of severe emphysema from other causes is noteworthy.

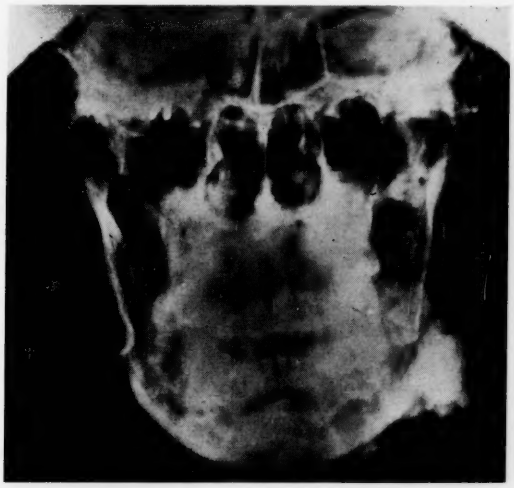


Fig. 38*D*.—Attached to the left mandible is a hard loculated mass. Overlying and below it is a multiloculated sebaceous cyst.

Roberts collected family data on cystic fibrosis of the pancreas which appear to be inconsistent with the quarter ratio predicted on the basis of the recessive hypothesis. The data were analyzed by several methods, but by all the frequency of the disease in sibships seemed to be higher than one can explain on the basis of the prevailing view of its inheritance. No suggestion of clinical disease in parents or in aunts and uncles was discovered.

Meconium ileus in the newborn and very young is a familiar manifestation of cystic fibrosis of the pancreas. Brown and his colleagues described onset of faulty evacuation of feces in 3 patients with cystic fibrosis of the pancreas. The onset of symptoms was at 22 months, 6 years, and 9 years, respectively.

Clark wrote about pancreatic atrophy in dogs, stating that the disease is relatively frequent in this species, manifesting itself in the first year of life. There seems to be little information on its genetic aspects (if any).

773. Liver. Monroe and Spencer, in discussing hereditary hemorrhagic telangiectasia, pointed out that Martini (1955) seems to have been first to emphasize the development of cirrhosis in the disease. Furthermore, they described a 62-year-old businessman with postnecrotic cirrhosis, esophageal varices, and gastrointestinal bleeding. Telangiectases are not the only source of bleeding in this disease.

X. BLOOD AND HEMATOPOIETIC SYSTEM

Disturbances of the Clotting Mechanism.—

774. Factor VII. Popham and Stevenson described a patient with idiopathic retroperitoneal fibrosis associated with a defect in factor VII. The connection between the two was uncertain, but retroperitoneal hemorrhage and subsequent fibrosis were discussed as a possibility.

Kupfer, Hanna, and Kinne studied a bleeder with factor VII deficiency. The inheritance was apparently that of an incompletely recessive trait. Presumed heterozygotes including both parents and relatives of both parents showed lesser deficiencies of this factor. The inheritance was autosomal recessive in two pedigrees of Cleton and Loeliger.

Hoag, Ageller, and Fowell studied the rate of disappearance of injected proconvertin (factor VII) in patients with congenital hypoproconvertinemia. Nour-Eldin found low factor VII and low factor VIII in members of the same family.

*775. Factor VIII.** Ikkala's monograph on hemophilia based on all ascertainable cases in Finland is a valuable contribution to match those of Bullock and Fildes (1911), Schloessmann (1930), Andreassen (1943), and Sköld (1944). On Dec. 31, 1957, 123 known hemophiliacs were living in Finland. In addition, one born in 1958 and 168 hemophiliacs who had died were included in the analysis.

*AHF (antihemophilic factor) and AHG (antihemophilic globulin) are used interchangeably for factor VIII in the discussion which follows.

Ikkala studied in detail a female with severe hemophilia A. Hemophilia had been known in her mother's family since early in the nineteenth century, and a brother had severe hemophilia A. The father was normal. Blood grouping did not exclude paternity. Mutation in the X chromosome contributed by the father was postulated. The incidence of male hemophiliacs alive on Dec. 31, 1957, was one per 17,000 males. Correcting for estimated incompleteness of ascertainment, the actual proportion was estimated at one in 13,000 to 14,000, the frequency in male livebirths at one in 6,500. Among living known hemophiliacs, Christmas disease accounted for 25 per cent, but in all liveborn hemophiliacs, it was estimated to represent 20 per cent; because of greater severity, hemophilia A is not represented in as high proportion in the group of living hemophiliacs. Ikkala collected the data from the literature and found that 15 per cent of hemophilic families and 18 per cent of unrelated hemophilic individuals in the reported series have hemophilia B. Complete pedigree charts are given for seventy-three families. It is noteworthy that this is the first large and detailed study of totally ascertained hemophilia which has appeared since heterogeneity in hemophilia was recognized (1952). The mutation rate per chromosome per generation was estimated at 3.2×10^{-5} for hemophilia A and 0.2×10^{-5} for hemophilia B.

Stefanovic, Rolovic, and Zujevic described hemophilia A with vaginal bleeding and bruising in a 2-year-old girl. Appropriate cross-correction tests confirmed the diagnosis. The father was thought to have a mild case; although clinically normal, he displayed diminished factor VIII. The mother was thought to be a carrier because she displayed some diminution in factor VIII and poor prothrombin consumption.

Quick discussed sporadic hemophilia, presenting a family in which the disease may have arisen by new mutation. He also presented a case of hemophilia in a girl with a negative family history and suggested new mutation as the mechanism. This is more difficult to accept, since two mutations are required—one in each parent—to result in a homozygous hemophilic female. Hemophilia A in females is usually either in the daughter of a hemophilic male and a carrier female or in a female who is of the XO sex chromosome constitution, i.e., suffers from the Turner syndrome (gonadal aplasia). It is to be hoped that chromosome analysis will be done in this important case; the subsequent history of the patient will also be of much interest. Quick further cites the fact that hemophilia A is about five times more frequent than hemophilia B as evidence that the mutation rate is higher in the former condition. Such is by no means necessarily the case. Other factors, such as the relative fertility of the hemophilic males and of the carrier females, are of great importance. Conclusions on mutation rate cannot be derived from frequency data without taking the factor of selection into account. Yet another statement difficult to fathom is the following: ". . . Sex-linked inherited diseases tend to die out by dilution."

Genetic aspects of hemophilia were reviewed by Vogel, especially, hemophilia in the female, the separation of hemophilia A and B, the mutation rate, primary gene action and its bearing on recognition of the female heterozygote and on substitution therapy, and autosomally inherited disturbances in AHG and PTC synthesis.

Abell and Bailey discussed hemophilic pseudotumor of bone which may simulate osteosarcoma. Webb and Dixon and also Tengberg, Ramgren, and Plengier discussed hemophilic arthropathy. Kaplan and his colleagues discussed dental care in the hemophiliac.

Rapaport, Patch, and Moore did assays of AHG in 35 obligatory carriers of hemophilia A and in 30 normal women. The normal women had a mean AHG value of 92 per cent of the reference plasma, the carriers 58 per cent. Both sets of data appeared to be normally distributed when the percentage values in log units were plotted on probability graph paper. One carrier with an AHG value of 22 per cent had had significant clinical bleeding. Seven with levels between 30 and 40 per cent had not. The authors suggested that about 2 per cent of hemophilia carriers can be expected to have AHG levels sufficiently low to lead to bleeding. Probability calculations indicated that AHG assay will detect about 75 per cent of true carriers in a potential carrier population and about 66 per cent of the normal members of such a population. Seemingly, the study gave no support to the view that the carriers in families with mild hemophilia A are paradoxically more likely to have low levels of AHG (Graham and coauthors, Am. J. M. Sc., 1953).

Bentley and Krivit also assayed AHG in carrier females. A modification of Quick's erythrocyte assay was used. Of 21 definite carriers and 5 probable carriers, 23 showed abnormally low levels.

Pitney and Arnold found low AHG in relatives of patients with von Willebrand's disease ("vascular hemophilia"). Perry, Opfell, and Baker observed a combined deficiency of PTA (¶446) and AHG in this condition.

Pitney and Elliott found that the concentrations of AHF are higher in white Australian patients with hyperglobulinemia due to various causes. Furthermore, healthy Australian aborigines had higher values than healthy Australian white persons, a finding which may also be related to the higher concentration of γ globulin in the aborigines (Curnow, 1957). That AHF concentration is related to γ globulin is unexpected, since AHF migrates electrophoretically with fibrinogen and is generally considered a β globulin. Cooperberg and Teitelbaum studied AHF concentration in relation to age.

Boudreaux and Frampton concluded that ingestion of peanuts or peanut flour prevents or aborts attacks of hemarthrosis. One of the authors is himself hemophilic. Peanuts had no effect on objective measures of the clotting defect.

776. Factor IX. The experience of Carter and colleagues indicated that Christmas disease can be a very severe hemorrhagic disorder, sometimes fatal despite administration of large amounts of blood and plasma.

Hemophilia A was discovered in dogs in 1946. Now, in Toronto, hemophilia B has been found in dogs (Mustard and colleagues). As with hemophilia A, genetically and pathologically the picture in dogs is identical to that in the disorder in man. All the dogs were Cairn terriers.

777. Factor X. Brody and Finch found that during a pregnancy, a woman with deficiency of factor X (Prower-Stuart) showed improvement in the labora-

tory and clinical signs of the deficiency. The possibility of the efficacy of hormone treatment in the nonpregnant state was suggested.

778. Others. Thompson and colleagues found a lack of the *Hageman factor* in 3 of 4 siblings of a family of Norwegian extraction. The pedigree pattern was consistent with autosomal recessive inheritance. As usual, the family was detected by the finding of a prolonged clotting time on routine test. Peking and Muscovy ducks, pigeons, turkeys, geese, and chickens appear to lack the Hageman factor. However, the serum of twelve common mammals tested plus that of three breeds of the horse corrected the defect present in this family and was therefore assumed to contain the Hageman factor. Kurkcuoglu and McElfresh studied a 9-year-old boy with Hageman factor deficiency. As in other reported cases, there were no hemorrhagic manifestations or other symptoms. Other cases were studied by Haanen and associates and by Loeliger and Hensen.

Shmerling, Jung, and Duckert and also Duckert, Jung, and Shmerling observed a new type of hereditary coagulation defect involving a "fibrin-stabilizing factor." Wound healing was poor. The family they studied had multiple consanguinity, and the inheritance of the defect was thought to be autosomal recessive.

In a woman with von Willebrand's disease, which behaved as an autosomal dominant trait in her family, bleeding into the peritoneal cavity from ovarian follicular cysts occurred and was sufficiently copious to require surgical intervention on two occasions (Tulloch, Alder, and Gillespsie).

779. Platelets. Gordon, Cassimos and colleagues, and Germain wrote about Aldrich's syndrome. Rivera and Biehusen described subperiosteal hemorrhage in the Aldrich syndrome—presumably the first report of a bone lesion. Motulsky pointed out that Aldrich's syndrome is a lethal disorder and that a relatively high mutation rate is to be expected. He estimated that one would expect a negative family history in as many as one-half of cases.

Nilsson and Lundholm had 2 patients with congenital thrombocytopenia associated with bilateral aplasia of the radius. Fourteen similar cases were found in the literature. Congenital heart disease and renal malformations occur in a considerable proportion. Aplasia of the radius occurs in some cases of the Fanconi syndrome (¶465), but it is distinguished by the bone marrow findings: the marrow is hypoplastic in the Fanconi syndrome, whereas megakaryocytes are present in normal or increased numbers in the syndrome discussed by Nilsson and Lundholm. One author has described the condition in 2 siblings.

Levine, Holcomb, and Lutzner observed a case of giant hemangioma in association with thrombocytopenia. About 20 cases have been recorded. Whether the background is genetic in any sense apparently remains to be demonstrated.

Raccuglia and Neel described a large family in which many members were affected with a hemorrhagic disorder: congenital vascular defect associated with a morphologic abnormality of the platelets and a deficiency of antihemophilic factor. The variability in the manifestations of the diathesis was very great. Some possibly affected individuals showed only a prolonged bleeding time. Autosomal

dominant inheritance was supported. The authors made suggestions for resolving the terminologic chaos which surrounds hemorrhagic disorders characterized by a prolonged bleeding time.

Gross and colleagues studied 4 patients with Glanzmann-Naegeli thrombasthenic thrombopathy. In one family, three generations had affected members. Clinically, petechiae, bleeding from mucous membrane, prolonged bleeding after injury, and severe anemia were features. Studies revealed prolonged bleeding time, abnormal capillary fragility, normal or increased number of platelets and megakaryocytes, and anisocytosis of the platelets, with giant platelets. Alteration in the concentration of several platelet enzymes was found.

Lausset, Colombani, and Colin studied two anti-human globulin sera in patients with idiopathic thrombocytopenic purpura, those with systemic lupus erythematosus, and those with pancytopenia. The first group of patients (6) reacted only with serum I. The latter two groups reacted with both serum I and serum II. Assuming that these are autoimmune diseases and that the γ globulin attached to the platelets and demonstrated by these tests is an autoantibody, one probably can conclude that there are at least two platelet antigens capable of inciting autoantibodies and that only one of the two is shared by other blood cells.

The White Blood Cells.—

780. Rossman and Hummer described chronic noncyclic neutropenia in 2 siblings. The neutropenia was observed over a period of 19 years in one sibling. The mother had systemic lupus erythematosus, and a sibling had died of bronchopneumonia after measles at age 15. Adrenal steroids seemed of genuine benefit in one of the neutropenic siblings. The other died at the age of 10 years before the availability of steroids.

Braun and colleagues and Lalezari and colleagues described familial neonatal neutropenia caused probably by fetomaternal leukocyte incompatibility and a mechanism comparable to Rh sensitization.

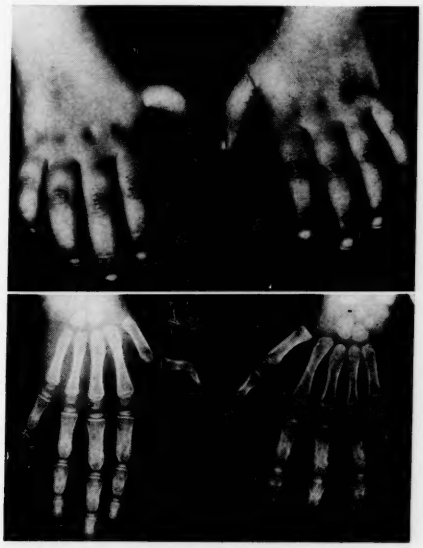
Andrews, McClellan, and Scott described a brother and sister with what they propose is a new disease appropriately called lethal congenital neutropenia with eosinophilia. Other hereditary neutropenic syndromes include the infantile genetic agranulocytosis of Kostmann (¶460), the Chédiak-Higashi syndrome (¶'s 137, 782), the familial neutropenia of Bousser and Neyde (Sang 18:521, 1947), and the Fanconi pancytopenia syndrome (¶'s 146, 465). (See Figs. 39 and 40.)

781. Leukemia. Latner and Zaki found that of 27 cases of leukemia, 12 (44 per cent) were of haptoglobin type 1-1. The difference from the normal was significant at a level of less than one per cent. (It is possible that the haptoglobin typing as 1-1 was inaccurate, especially if hemolysis was present. That a true association has been demonstrated remains to be confirmed.)

Steinberg studied the families of 249 patients less than 16 years old at the time of diagnosis of acute leukemia. He found no evidence for an increased frequency of leukemia, cancer of all types, pernicious anemia, or other blood

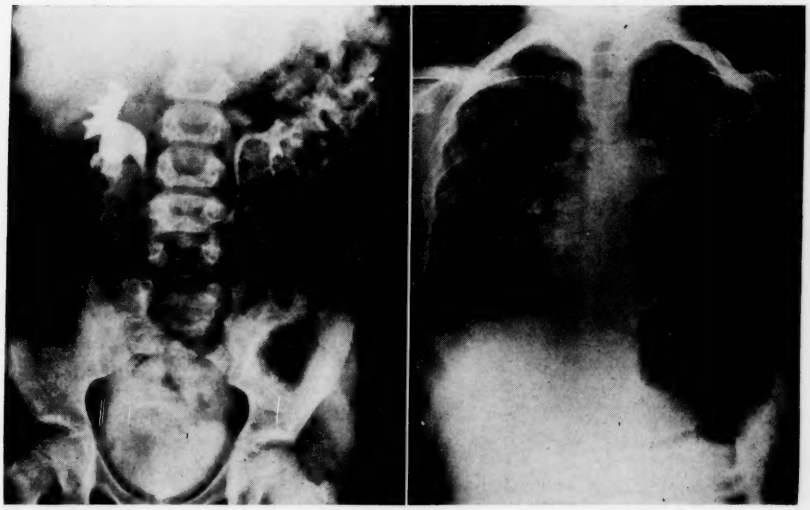
Fig. 39.—Fanconi's anemia. F. L. (653621) has hypoplastic anemia with little or no change in leukocytes and platelets. A variety of congenital malformations are present. No similar disorders are known in the family. The anemia has responded satisfactorily to cortisone. (Courtesy of Dr. William H. Zinkham.)

A.



B.

Fig. 39*A* and 39*B*.—Peculiar right thumb.



C. *D.*

Fig. 39*C* and 39*D*.—Right hydronephrosis, spina bifida occulta, and probably a cardiac malformation.

dyscrasias in these families. There were no relation to birth order, no relation between maternal age and the age of onset, and no relation between onset or death and season of the year. There was no association with a particular blood group of the ABO or Rh systems.

782. Davidson, Milner, and Lawler described a "new" inherited autosomal dominant anomaly of the white cells—giant neutrophil leukocytes—in 7 members of three generations of a family.

Undritz reviewed morphology and genetics pertaining to hereditary constitutional anomalies of leukocytes.

Spencer and Hogan described the Chédiak-Higashi syndrome in a white male child, the offspring of a first cousin marriage. Manifestations were hepatosplenomegaly, frequent pyogenic infections, generalized lymphadenopathy, partial albinism, and (with Wright's stain) magenta-colored cytoplasmic inclusions of the lymphocytes and polymorphonuclear leukocytes. Gilloon, Pease, and Mills studied a case.

The Erythron.—

783. Nilsson and Lundholm described 3 siblings with the Fanconi syndrome (Figs. 39 and 40). One had chronic pancytopenia, abnormal pigmentation, stunted growth, deformity of the upper limbs, and kidney anomalies. The other 2 siblings had only the blood changes. McDonald and Goldschmidt described 3 siblings and 2 other patients with pancytopenia and congenital defects (Fanconi's anemia). Two of the patients had impalpable radial pulses. A useful review of the associated anomalies was provided.

784. Wise and Loker described a large family with many persons affected by spherocytic anemia. In the family, a total of eleven splenectomies have been performed to date. Carruthers studied a family with mild disease.

Crosby and Conrad concluded that the abnormal shape alone is not responsible for the destruction of the erythrocytes of hereditary spherocytosis in the spleen. They subjected 2 healthy young men with this condition to repeated phlebotomy until iron deficiency anemia developed. Although the erythrocytes lost their spherical shape and became thin and less fragile, their life span was not increased. Splenectomy resulted in increased red cell life span and correction of the hemolysis, but spherocytosis persisted. It is of interest that neither subject was anemic, that is, both had "compensated" hemolytic disease, and in one, the rate of production of hemoglobin was estimated to be twenty times normal!

Griggs, Weisman, and Harris studied alterations in osmotic and mechanical fragility related to in vivo erythrocyte aging and splenic sequestration in hereditary spherocytosis. Red cells from removed spleens displayed increased fragility and reduced in vivo survival. The findings are consistent with the view that red cells are trapped in the spleen because of their anomalous shape and undergo changes resulting in increased fragility, possibly in part the result of unfavorable conditions of oxygen tension. The beneficial effects of splenectomy are explained by these studies.

Features of identity between hereditary spherocytosis in the deer mouse and in man were reviewed by Anderson, Huestis, and Motulsky. Affected mice are even subject to gallstones as are affected men. The only different feature is recessive inheritance of the disease in the mouse. The possibility of fundamental heterogeneity with existence of a recessive form of the disease in man was discussed. The recessive transmission of the murine disease may indicate a difference in the biochemical defect or may be an instance of "dominance modification" (R. A. Fisher: *The Genetical Theory of Natural Selection*). Natural selection may be more rigorous in mice than in men and might result in a genome permitting expression of the gene only in the homozygous state.

Allison, Kates, and James speculated that the primary defect in hereditary spherocytosis might involve an element of the cell membrane, such as phospholipid. Therefore, they studied the in vitro incorporation of P^{32} into phospholipid of the erythrocyte. Over-all synthesis and turnover were the same as in cells from normal individuals. However, the spherocytic cells showed labeling in (1) an increased proportion of lysophosphatidyl ethanolamine and (2) a reduced pro-

Fig. 40.—Fanconi's anemia. This family illustrates the occurrence of acute leukemia and aplastic anemia in siblings as mentioned in ¶465.

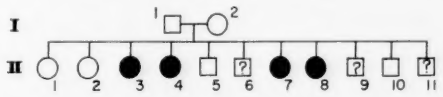


Fig. 40*A*.—The pedigree. The parents, I 1 and I 2, are undoubtedly unrelated; the father was born in Ireland and the mother in West Virginia, of Old American parents. Individuals II 3 and II 4 died at ages 10 months and 8 years, respectively, of leukemia. Three male siblings (II 6, II 9, and II 11) died in the fetal or neonatal period. Two female siblings have been under the care of the Johns Hopkins Hospital for Fanconi's pancytopenia. One (II 8, T. C., 755742) died at the age of 14 years with hemorrhage from many sites and septicemia. Anomalies included a café au lait area 6 by 4 cm. in size on the anterolateral aspect of the right thigh and a pelvic kidney. The second (II 7, A. C., 716095) still lives at the age of 20 years with only mild to moderate pancytopenia (Hct 36 per cent, WBC 2,100 per cubic millimeter, platelets 106,000 per cubic millimeter). Both sisters are small with generalized osteoporosis.

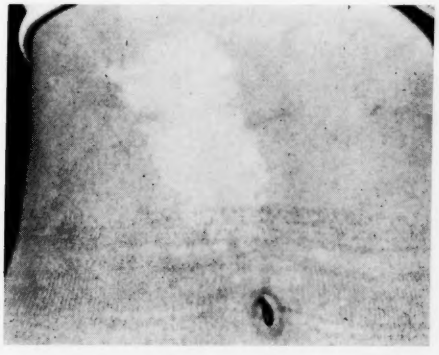


Fig. 40*B*.—The second sister has a large area of depigmentation on the anterior abdominal wall and also fusion of certain of the bones of the wrist.

portion of phosphatidyl ethanolamine as compared with normal. These workers suggested therefore that a partial enzymatic block in the conversion of the first to the second is the basic defect in spherocytosis. However, Prankerd expressed difficulties "in accepting their hypopthesis of a causal relationship between the lysophosphatide content and the shape of the red cells as the primary genetical defect in the disease."

785. Conrad, Crosby, and Howie described hereditary nonspherocytic hemolytic disease. They pointed out that without red cell survival studies, the mildy affected patients are completely indistinguishable from those with Gilbert's constitutional hepatic dysfunction. Unfortunately, glucose-6-phosphate dehydrogenase activity of the erythrocytes was not determined. Of their 20 patients, 19 were male. However, since the work was done in a military installation, the sex ratio of the patient series cannot be used as evidence that many of them had the type of chronic nonspherocytic hemolytic disease described in ¶734.

Tönz, Mereu, and Käser studied familial nonspherocytic hemolytic anemia in 2 brothers, ages 7 and 14.

De Gruchy and colleagues also discussed nonspherocytic congenital hemolytic anemia. Among the hereditary hemolytic anemias, one can now distinguish (1) the thalassemias, (2) hereditary spherocytosis, (3) the hemoglobinopathies, (4) elliptocytosis with hemolytic anemia, and (5) nonspherocytic hemolytic anemia with a defect of glucose-6-phosphate dehydrogenase. A residual group remains, however.

786. Clarke and colleagues demonstrated linkage between elliptocytosis and the Rh factor in two families. No recombinant individuals were identified in either family. Of interest is the fact that one proband was a west African Negro. In this family sickling also occurred, and linkage with blood group P was suggested—a finding which it will be of interest to study in other pedigrees.

Kuroda, Takeuchi, and Nagamori could not demonstrate linkage with the Rh factor in a Japanese kindred with elliptocytosis associated with hemolytic anemia. They concluded that the type of elliptocytosis in this family is the nonlinked variety, described by Morton.

787. Dunsford and Owen, contrary to previous studies, could find no evidence for strong association between blood group O and acquired hemolytic anemia in a series of 127 patients.

788. In the not distant future, the evidence will be sufficiently conclusive and the information sufficiently detailed to justify inclusion of at least some of the *thalassemias* among the hemoglobinopathies (see ¶469). For the present, however, they will be discussed as a group, separate from the hemoglobinopathies, as in previous reviews.

McFarland and Pearson described heterozygous thalassemia (thalassemia trait) in non-Mediterranean families. The ethnic backgrounds included Danish, English, Scottish, Filipino, and Negro.

Weatherall and Vella described thalassemia in a Gurkha (Nepalese) family. Jackson, Lehmann, and Sharih found thalassemia in a Tibetan.

Smith concluded that splenectomy in thalassemia increased the ease of maintaining the level of the blood with transfusions. The survival of transfused cells was increased even though there was no change in the survival of the patient's own cells.

789. Giles found an excess of blood group A in a large group of patients with megaloblastic anemia of pregnancy. A similar excess has been found in pernicious anemia.

Siurala, Erämaa, and Nyberg found that the incidence of pernicious anemia and of gastric carcinoma is about the same in relatives of probands with pernicious anemia or with atrophic gastritis.

790. Scott and his colleagues described hemolytic disease which resembled that reported by Schmid, Brecher, and Clemens (¶466), especially in the presence of red cell inclusions and abnormal excretion of a urinary pigment. Differences were the presence of a variant hemoglobin and the failure to find more than one case in the family.

The hemoglobinopathies: 791. Rossi gave a general review. Techniques in the identification of variant hemoglobins were discussed by Huehns and Jakubovic, among others. Gratzer and Beaven described the application of transparent starch gels to the study of hemoglobins.

Perutz and colleagues discussed the structure of hemoglobin, and in a companion article, Kendrew and colleagues provided a similar analysis of the structure of myoglobin.

Muller succeeded in separating the α and β chains of adult and fetal hemoglobin on starch gel electrophoresis.

Robinson and Itano have succeeded in recombining the α and β chains of human adult hemoglobin and canine hemoglobin. The method can be used in identifying whether the α or β chain is the site of the defect in an abnormal hemoglobin. The advantage of canine blood over human hemoglobin variants is that it is available in large quantities and differs from human hemoglobin in both chains. Whether the defect of the human hemoglobin variant is in the α chain or the β chain, the recombinant form with canine hemoglobin is likely to have a different electrophoretic mobility.

Huisman and Meyerling and also Meyerling and colleagues studied the heterogeneity of human and animal hemoglobins by means of carboxymethylcellulose and Amberlite IRC-50 chromatography. In normal adults, they found Hb A_1^A, Hb A_1^B, Hb A_1^C, Hb A_0, Hb F, and Hb A_2 as well as a yellow fraction representing methemoglobin reductase. They found two fetal hemoglobins in normal individuals as well as heterogeneity in Hb S and E.

792. Hb A_2. Heller, Josephson, and Singer described a method for the rapid demonstration of Hb A_2 by means of agar gel electrophoresis. Heller, Yaku-

lus, and Josephson demonstrated that Hb A_2 has a specific antigenicity in addition to its specific physical properties.

By "fingerprinting" (see ¶473), Muller and Jonxis demonstrated that in Hb A_2, a different polypeptide chain is substituted for the β chain of Hb A (A_1, if you will). The second chain of Hb A_2 is denoted the δ chain, and the formula becomes $\alpha_2 \delta_2$. The differences between the β chain of Hb A_1 and the δ chain of Hb A_2 are less than those between the β chain of Hb A_1 and the γ chain of Hb F.

793. Hb S. Ober and colleagues described a case of fatal intravascular sickling in a patient with sickle cell trait. Occlusion of mesenteric vessels led to death. There was no suggestion of what had precipitated intravascular sickling.

Ryan and colleagues found no deviation in the frequency of persons with Hb SA among tuberculous Negroes from what would be expected from population figures and no difference in the clinical behavior of tuberculosis in persons with Hb SA and AA. Rahimtoola, Good, and Davies studied pulmonary infarction as a complication.

Bernstein and Whitten studied the renal histopathologic condition in sickle cell anemia. The inability to concentrate the urine is probably related to alterations in the medullary pyramids (edema, telangiectasia, scarring, and obliteration of tubular elements) which are in turn secondary to localized ischemia. Glomerular enlargement and increased vascularity in juxtamedullary glomeruli are believed to provide a basis for elevation of glomerular filtration rate and renal plasma flow. Later changes in the glomeruli can well account for the progressive renal insufficiency shown by some patients.

Schlitt and Keitel gave a useful review of the renal manifestations of sickle cell disease, sickle cell trait, SC disease, and sickle-thalassemia. Hyposthenuria is the earliest functional defect and is found in almost all patients with sickle cell anemia and in a majority of those with sickle cell trait. They concluded that until the mechanism by which urinary concentration is normally accomplished by the kidney is understood, the mechanism of sicklemic hyposthenuria will not be known. At least 3 cases of the nephrotic syndrome in patients with sickle cell anemia have been reported; we have seen one such patient.

Levitt and colleagues discussed the defect in urine concentrating capacity which is present both in sickle cell disease and with the sickle cell trait. They state that it does not occur in chronic anemia of other causation. It is, they consider, entirely consistent with modern views on the concentrating mechanism.

Hilkovitz described bone marrow failure in 3 siblings with sickle cell anemia.

Manfredi and colleagues determined the peripheral arteriovenous oxygen difference in sicklemic patients in crisis and during intercritical periods. In crisis, relative arteriolization of venous blood was demonstrated, caused, apparently, by bypasses in the superficial circulation. A neurogenic mechanism might, in the opinion of these workers, be a precipitating factor in sickle cell crisis. Pharmacologic methods for interrupting a neurogenic mechanism would seem worthy of exploration. Jensen, Rucknagel, and Taylor consistently found more sickle cells in venous blood than in arterial blood. They suggested that the high cardiac output (and probably the arteriolization referred to) is effectively compensatory.

Undritz, Betke, and Lehmann studied the erythrocyte sickling which occurs in some deer. It had been previously observed that the sickling was produced by passing oxygen through the blood and that sickling so produced was reversed by the reducing agents $NaHSO_4$ and $Na_2S_2O_5$—a behavior opposite to the sickling phenomenon in man. However, further study indicated that sickling was equally well produced by saturation of the blood with nitrogen or carbon monoxide but not with carbon dioxide. The action of oxygen, nitrogen, and carbon monoxide is a replacement of carbon dioxide and the creation of in vitro "respiratory alkalosis." The reducing agents mentioned are acid. Consequently, pH appears to be the critical factor in sickling of the red cells of the deer.

Priapism in sickle cell anemia was successfully treated with low doses of estrogen (Erman and Bloomberg).

Munro and Walker discussed the ocular manifestations of Hb SC disease, with main reference to the aneurysmal changes in the retinal vessels which were described also by Smith and Conley (1959). Geeraets and Guerry found angioid streaks, apparently similar to those of pseudoxanthoma elasticum, in 5 of 69 patients with sickling examined. In 2 the hemoglobin was SS, in 2 it was SC, and in one electrophoresis was not performed.

In enucleated eyes, histologic changes were found not only in Bruch's membrane but also in arteries. These workers then investigated at autopsy 16 patients with sickle cell disease and found "elastic tissue degeneration" in arterial walls of 2.

Anderson and colleagues, in studying pregnant patients with sickle cell disease and sickle cell–Hb C disease, concluded that the maternal and fetal hazards are less than other reports have suggested (¶477).

794. Hb C. Galbraith and Green found CC disease in a 66-year-old white man of Anglo-Saxon ancestry. A half brother and both of the patient's sons had AC.

795. Hb D. McCurdy reported a Negro with sickle cell–Hb D disease. The clinical picture was essentially identical to that of sickle cell disease. Martin and colleagues described the first family with Hb D in Germany and Gouttas and co-workers the first from Greece.

796. Hb E. Gouttas and colleagues described 2 sisters with severe anemia that resulted from the coincidence of the genes for thalassemia (derived from the mother) and for Hb E (derived from the father).

Aksoy estimated that 1.37 per cent of Eti-Turks have Hb E, previously described mainly in southeastern Asia, India, and Ceylon. He proposed this finding as evidence of a relationship between the Eti-Turks and the Indians. From families in which the genes for both Hb S and E were segregating, Aksoy concluded that Hb S, E, and A are either allelomorphic or closely linked. Hb E was described in Bengalese by Swarup, Ghosh, and Chatterjea.

From their known distribution, Yamaoka expected to find Hb E and thalassemia in Japan but in a large survey found none.

797. Hb F. Matsuda and colleagues concluded there is no "embryonic" or "primitive" human hemoglobin which precedes fetal hemoglobin in ontogeny the way fetal hemoglobin precedes adult hemoglobin. However, Butler, Flynn, and Huehns presented findings which they suggest indicate the presence of a distinct "embryonic" hemoglobin present before 9 weeks and not afterward. The embryonic hemoglobin showed different electrophoretic mobility and a different rate of denaturation. Zilliacus similarly presented evidence he interpreted as indicating the existence of an embryonic hemoglobin.

Immunologically, utilizing Ouchterlony agar precipitin plates, McCormick and Walker distinguished three types of fetal hemoglobin.

The observations by Thomas and colleagues on hemoglobin synthesis in cell suspensions from liver and bone marrow of a 17-week-old and a 9-week-old fetus appear to dispose of the notion that fetal and adult hemoglobins are synthesized in different tissues. Their studies provided no answer to the question of whether the two types of hemoglobin occur in the same or different red blood cells.

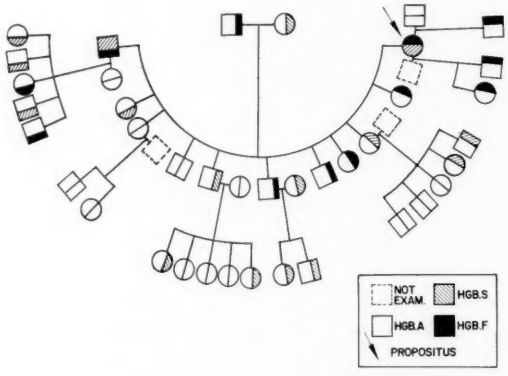


Fig. 41.—Hemoglobin phenotypes in a family with both sickle cell trait and persistent fetal hemoglobin. The point of importance is that persons with both traits transmitted only one or the other to children, never both. This is interpreted to indicate that the genes for the two traits are allelic and that a defect in production of β chains is the basic fault resulting from the gene for persistent fetal hemoglobin. (From Bradley, T. B., Jr., and Conley, C. L.: Tr. A. Am. Physicians 73:72, 1960.)

The factors that determine switching from predominantly fetal hemoglobin synthesis to predominantly adult hemoglobin synthesis may be elucidated by the work of Allen and Jandl. The relative proportions of the two hemoglobins synthesized in vitro by reticulocytes of cord blood could be influenced by environmental manipulations. Oxygen lack, glucose deficiency, and perhaps valine deficiency stimulated production of fetal hemoglobin.

Herman and Conley studied three generations of a Negro family in which fetal hemoglobin persisted in adults. Sickle cell hemoglobin was segregating in the same family. The hereditary factor responsible for persistence of fetal hemoglobin appeared to be allelic with Hb S and C. The authors suggested that the primary action of the gene was to prevent the formation of Hb A, with the result

that fetal hemoglobin persists in its stead. Interestingly, doubly affected persons (with one allele for sickle cell hemoglobin and the other for fetal hemoglobin persistence) showed no clinical or hematologic abnormality although the hemoglobin was predominantly of the sickle cell type. Apparently the presence of Hb F results in resistance to sickling.

Bradley and Conley described five families, all Negro, in which fetal hemoglobin persisted into adult life. (One of the five was the family reported by Herman and Conley.) In two families, sickle cell hemoglobin was also present. Persons with both sickle cell hemoglobin and fetal hemoglobin transmitted one or the other but not both to their children (Fig. 41). It was concluded by these workers that the primary genetic defect in persons with fetal hemoglobin persistence is at the β chain locus and that the effect of the mutant gene is to prevent the formation of functional β chains so that Hb A is not produced. The appearance of fetal hemoglobin is a secondary phenomenon. Unlike the situation with Hb Bart's (which is γ_4) and Hb H (which is β_4), α_4 is not formed.

McCormick and Humphreys described high fetal hemoglobin–Hb C disease. This is probably the same condition as the persistent fetal hemoglobin state described by Conley and co-workers. Unlike the situation when combined with Hb S, Hb FC disease is accompanied by anemia.

Among 100 newborn Nigerian babies, Hendrickse and co-workers found "fast" hemoglobin fractions in 11. In 3 studied in detail, the fast hemoglobin resembled Hb Bart's in one and that of Fessas and Papaspyrou in 2.

Raper, Ager, and Lehmann discussed the "fast" fetal hemoglobin described by Fessas and Papaspyrou and suggested the designation Hb Singapore-Bristol. In Birmingham, Barrow and Kohler found Hb Bart's in a West Indian girl. It had disappeared by the age of 15 weeks.

Huehns and colleagues modified the starch gel technique in such a way as to separate Hb A, Bart's, and H when present together. In 2 previously reported adults with Hb H, Hb Bart's was also found in small amounts. This may suggest that the α chains of fetal and adult hemoglobin are under identical genetic control.

Lie-Ingo and Jo found a fast-moving fetal hemoglobin as the major component in a case of hydrops fetalis. Neither parent showed an electrophoretically abnormal adult hemoglobin; however, both had hematologic changes of thalassemia minor. No fetomaternal incompatibility of erythrocyte antigens was demonstrated, and the authors suggested that hemoglobin incompatibility was responsible for the pathologic changes in the fetus.

Sen, Das, and Aikat studied fetal hemoglobin of the monkey.

798. Hb G. Shooter and colleagues provided detailed electrophoretic characterization of Hb G on the basis of material from a patient with homozygous Hb G disease (and his family) discovered in a survey in Ibadan, Nigeria. They doubted that the hemoglobin described by Schwartz and others (1957) as Hb G is in fact the same as the hemoblobin they studied or the same as the original Hb G described by Edington and Lehmann in 1954. They suggested that Schwartz' hemoglobin may be Hb Q (Vella and coauthors, 1958).

Schneider and Haggard described Hb G in heterozygous state in several members of a family. No clinical or hematologic abnormalities were present. By different methods, Hb G represented 40 to 75 per cent of the total hemoglobin. They pointed out that a reported homozygous individual was also normal. Hb G can then be considered a normal variant.

Atwater, Schwartz, and Tocantins described a family in which some members had four distinct electrophoretic components. The four components seemed to be Hb A, C, G, and X or Porter (the name of the family). It was suggested that the last might be $\alpha_2^G \beta_2^C$.

Raper and colleagues studied 2 relatives who had four hemoglobins: A, G_{Br} (for Bristol, England, where Raper works), C, and a new hybrid hemoglobin, G_{Br}/C. The pedigree demonstrated independent segregation of Hb C and G_{Br}. Hb G_{Br} has an α chain lesion, Hb C a β chain lesion. The authors suggested that the relative proportions of G_{Br} and C suggest that the final step in hemoglobin synthesis is association of α_2 and β_2 subunits.

799. Hb H. In a person of southern Italian origin, Bütikofer and colleagues found hemolytic anemia, red cell inclusions, and Hb H by electrophoresis. The presence of thalassemia in the family was established in the mother and brother, who had thalassemia minor with increased Hb A_2.

Dittman and colleagues described Hb H in a woman of Sardinia whose mother and son had the thalassemia trait. The woman herself showed features of the thalassemia trait. There was no elevation of Hb A_2 in this family. Erythrocyte inclusions of Hb H were demonstrated by vital staining with brilliant cresyl blue. The findings are probably consistent with the possibility of an α chain mutation which is in heterozygous form in those members of the family with only the thalassemia trait and is homozygous in the woman who also showed Hb H.

800. Hb I. Atwater and colleagues described sickling (of somewhat atypical type) in a Negro patient with thalassemia–Hb I disease without Hb S. Thalassemia was inherited from the mother. Hb I was probably inherited from the father, who was not available for study. In the patients of Rucknagel, who first discovered Hb I, sickling did not occur. However, the abnormal hemoglobin constituted only about 20 per cent of the total rather than 70 per cent as in Atwater's patient. The presence of thalassemia probably reduced the amount of Hb A and accounted for the increased proportion of Hb I. This is the only reported example of sickling in the absence of sickle cell hemoglobin.

801. Hb J. Wasi, Githens, and Hathaway found Hb J in an American Caucasian father and son of Swedish ancestry. This hemoglobin was first found in an American Negro by Thorup and colleagues in 1956. Jim and Yarbro observed it in a Hawaiian-Chinese-Caucasian male.

802. Hb M. Gerald, Efron, and Pease demonstrated the presence of an altered amino acid sequence in Hb M (Boston type). The substitution is

apparently a tyrosyl residue. This is the first demonstration that an amino acid change can result in anomalous spectroscopic behavior.

Hansen, Jagenburg, and Johansson studied an Hb M. In a man and child in Leipzig, Betke, Gröschner, and Bock discovered a type of Hb M which differed in its spectrophotometric and reaction characteristics from Hb M_S (Saskatoon, studied by Baltzan and Gerald), M_B (Boston, studied by Gerald), and M_M (Milwaukee, studied by Pisciotta and colleagues, J. Lab. & Clin. Med. 54:73, 1959). They proposed to call it Hb M_L (Leipzig) and suggested from its properties that it may be identical to the Hb M which was studied by Hörlein and Weber and which is historically significant as the first identified hemoglobin variant. Yamaoka and colleagues and Kimura and colleagues described an Hb M in Japan.

803. Hb O. Ramot and colleagues described Hb O in an Arab family, the first time it has been found outside Indonesia. The sickle cell trait was also present, and some individuals had Hb A, S, and O. The authors concluded, however, that the lesion is not in the α chain in both Hb P and O.

804. Hb P. Lambotte-Legrand and colleagues found Hb P, S, and A in a native of the Congo, indicating that Hb P is in a different genetic series from Hb C and S, that is, not allelic.

805. Unlettered hemoglobins. Itano and Robinson demonstrated that Hb Hopkins 2 (¶156) is abnormal in its α chain and normal in its β chain, in contrast to Hb S, which is normal in its α chain and abnormal in its β chain. Family data of Bradley, Boyer, and Allen (1961) indicate that the gene defects are not allelic and probably not closely linked. Two hemoglobin loci, one for the α chain and one for the β chain, are suggested. Presence of a normal and an abnormal allele at each locus probably results in four hemoglobins in the same individual: normal, doubly abnormal, and the two singly abnormal. Independent synthesis of the α chains and β chains in pairs at independent sites is suggested. Each allele is responsible for the synthesis of *two* α chains or *two* β chains.

Huisman, working in Augusta, Georgia, found an abnormal adult hemoglobin he calls Augusta I, which appears to be a tetramer of the β chains of sickle cell hemoglobin, and one called Augusta II, which appears to be a tetramer of the β chains of Hb C. A defect of the α chain is postulated. The father, aunt, and 3 siblings had three hemoglobins, S, A, and H. The propositus had five hemoglobins, A, F, Augusta I, S, and H. The level of Hb A_2 was normal. To explain these findings, Huisman suggested that the α chains of fetal and adult hemoglobin are under independent genetic control.

In Japan, Yamaoka and colleagues found what may represent a new hemoglobin. Presumably, the practice of naming it for the city or institution where it was discovered until its possible identity with other hemoglobins can be checked will be followed. The workers are at Kyushu University in Fukuoka.

806. Miscellaneous. Zuckerkandl, Jones, and Pauling compared the patterns of tryptic peptides derived from various animal hemoglobins. Primate

hemoglobins showed patterns rather similar to those known for man and rather different from those in other forms. The workers speculated on the mutability of genes. "In addition to natural selection, the thermodynamic stability of the genes themselves may be an important factor in determining the distribution of alleles in a population. Our results indicate that stable hemoglobin genes had been developed before the separation of humans and anthropoids from their common stock." The authors suggested that the mutant gene may be less stable than the "normal" gene and that this may explain why in instances like Hb S and C, the abnormality is at the same amino acid—C may be a mutant derived from S. The geographic distribution of Hb C is consistent (¶477).

Surveys of hemoglobin types were conducted in Caingang Indians of Brazil (Tondo and Salzano), in Chinese residing in Singapore and its environs (Vella), in Hawaii (Jim and Yarbro), and in San Blas Indians (Eisen and Abildgaard).

Popp and St. Armand presented evidence for codominance of mouse hemoglobin types, as in man. At least one mouse hemoglobin locus is closely linked to albinism in linkage group I. Variant hemoglobins were observed among wild mice.

Davenport discussed the hemoglobin which occurs in the root nodules of legumes. Studies of this by techniques like those used for human and animal hemoglobins would be fascinating.

Blood Groups.—

807. Morgan presented his important work on the biochemical genetics of blood group specificity (¶491) as the Croonian Lecture for 1959.

Race gave a readable invitation lecture at Columbia entitled "Blood Groups and Human Genetics." Some of the interesting matters considered follow. That any blood group behaves as a recessive trait (P^k of the P system is a possibility) is doubtful. Race now subscribes to the view that the Rh system, rather than being determined by closely linked genes C, D, and E, is specified by a cistron with several hundred mutational sites. He pointed out that the donor in whom a new blood group antigen, Sw^a, was found by Cleghorn (¶494) is a contemporary pianist, Donald Swann. Another personal point of interest was that the family of "a most distinguished geneticist, the Professor of Botany at Oxford" (presumably Darlington) is one of the relatively unusual ones in which secretor-Lutheran linkage is demonstrable (Heredity 12:513, 1958) because of the occurrence of one parent (the geneticist's wife) who is heterozygous for both factors. Race mentioned the finding in a true hermaphrodite (with normal female karyotype) of a bizarre ABO group described previously only in the horse; the normal karyotype was a disappointment. Four examples of environmental modification of blood type were mentioned: (1) There is loss of type A agglutinability in leukemia. (Race thinks this is not somatic mutation.) (2) In more than 20 patients, as a result of disease, usually of the lower bowel, e.g., carcinoma of the colon, a B-like antigen was acquired by the red cells. An unproved theory is that a particular strain of *E. coli* which contains a polysaccharide like human blood group B substance releases this polysaccharide into the circulation, where it becomes attached to the red cells. (3) Chimerism occurs in dizygotic twins who accidentally

have interchange of blood in utero. (4) Occasionally, in women who are Le (a+), there is complete loss of the antigen Le^a from the red cell during pregnancy, with return after delivery.

Vogel, Pettenkofer, and Helmbold reviewed evidence bearing on the hypothesis that carriers of various ABO blood groups display different responses to the bacteria and viruses responsible for certain epidemic diseases widespread in the past and that such may be a major cause of geographic variations in A, B, and O genes as observed today. (1) *Pasteurella pestis* has an antigen similar to the H_0 antigen. Persons who because of their own H antigen are unable to make anti-H antibody might have a particularly poor prognosis in case of an infection with plague. The O gene is frequent in places where little or no plague has occurred and rare in plague areas. (2) The smallpox virus has an antigen similar to the A antigen. Humoral resistance to smallpox would be expected to be more effective in patients of blood groups B and O, who carry an anti-A antibody in the serum. The geographic distribution of the A gene in the Old World supports the hypothesis of a selective disadvantage with respect to smallpox. (3) In older reports, it seems that although susceptibility to syphilis is uninfluenced by blood group, patients of blood group O have a better chance of becoming seronegative with treatment. The high frequency of group O in the Indians of Central and South America may be related to more effective resistance to treponematous infections.

Livingstone and Motulsky separately discussed the same matters (¶664). Livingstone communicated to Vogel that in West Africa, blood group A had higher frequency in a group of severely pock-marked persons.

Practical aspects of the use of blood grouping for paternity testing were discussed by Sussman.

Population surveys of blood groups are too numerous to enumerate exhaustively here. Included were studies in Korea by Won and colleagues, in New Britain by Simmons, Gajdusek, and Larkin, in the Penobscot Indians by Allen and Corcoran, and so on.

Madeleine Smith reviewed the subject of paleoserology, the determination of blood groups on bones and mummified tissues from the ancient dead. One wonders whether the antigenic characteristics of bacteria in mummified tissues could be investigated for elucidation of the important question of what changes have occurred in such organisms through the ages.

808. The ABO system. Koscielak and Zakrzewski demonstrated that blood group A substance separated from human erythrocytes has chemical composition and properties quite different from the blood group substance obtained from body fluids.

Andersen presented evidence for the existence of an allele in the blood group A series which determines weak group B specificity in addition to group A. He proposed the designation A^b and considered it a subgroup like A_1 and A_2.

Sussman, Pretshold, and Lacher described what they interpreted to be the same group that Moullec called group B_3. It was discovered during routine matching when an apparent discrepancy in Landsteiner's law was observed: the cells

were group O but the serum had only anti-A antibodies. The mother of the proband showed the same atypical blood group.

Chung, Matsunaga, and Morton studied the ABO polymorphism in Japan in order to test hypotheses that have been developed on the basis of Caucasian material. The Japanese samples are large; they provide information on blood group B, which is rarer in Caucasians; interpretation is simplified by the absence of A_2; the Japanese have had higher death rates in the recent past and have therefore possibly been under more intense selection than have the populations of Europe and America. They found a significant reduction in fertility with ABO incompatibility. An interesting Caucasian-Japanese difference concerned the effect of parity: in the Japanese, the decrease of incompatible children with parity seen in Caucasians and interpreted as consistent with isoimmunization in previous pregnancies was not observed. "Apparently heteroimmune mechanisms are more important in Japan, prompting the suggestion that human populations may be now changing from an environment in which selection was primarily due to heteroimmune antibodies (represented by the Japanese sample) to one in which isoimmunization is more important, initially for O mothers and perhaps subsequently for non-O mothers."

ABO fetomaternal incompatibility was discussed by Dyggve and Munk-Andersen, by Hubimont, Bricoult, and Ghysdael, and by Wiener and colleagues. Wiener studied fifty-one families. In fifty, the mother was blood type O. All babies were either A or B. There was only one A_2 infant, consistent with the low antigenicity of this type. In the infant, fathers, and siblings, there was an abnormally low frequency of nonsecretors. The antigens of the secretions have been shown to be potent sensitizers. Unlike the situation with Rh incompatibility, a first offspring may be severely affected in this type of sensitization.

Geczy described a case of hemolytic disease of the newborn evoked by group A_1 in the offspring of an A_2 mother.

Buckwalter, Scoy, and Knowler studied ABO blood groups in sibships containing one or more members with peptic ulcer. As in the earlier study of Clarke and colleagues in Liverpool, the results were in the direction supporting a causal nature of the O-ulcer association (p value between 0.05 and 0.10).

Vyas, Bhatia, and Sanghvi described three instances of weak blood type B in an Indian family. B and H antigens in the saliva and H of the red cells were normal. The authors suggested that direct transmission from father to son ruled out a rare recessive "suppressor" (comparable to "Bombay") as the mechanism and suggested instead that the atypical B is due to an allele in the ABO series. No information was given relative to the possibility of consanguinity to account for father-son transmission of a recessive trait.

Marsh discussed the pseudo-B antigen which develops "in vivo" in group A_1 cells as an acquired character. It is thought to develop as a result of in vivo action by bacterial enzymes.

Schertz, Jurgelsky, and Boyd concluded that a one locus difference is responsible for the presence or absence in lima beans of the agglutinin for human erythrocytes of blood group A_1. The f_1 progeny from a "high" line by a "low" line were all high. The f_2's from selfing of f_1 resulted in the ratio of three highs

to one low. In the high female by low male cross, there was skew to the high side. Several possible explanations for the last observation were offered.

809. The Rh system (Wiener, Unger, and Sacks). Cohen presented data indicating a deficiency of ABO-incompatible matings in an Rh-sensitized, Rh-incompatible series and an excess of ABO-incompatible matings in an Rh-non-sensitized, Rh-incompatible series. Possible biologic mechanisms underlying the superiority of the doubly incompatible matings and the possible impact of the ABO-Rh interaction on allele frequencies in future generations were discussed.

Masouredis studied the $Rh_0(D)$ antigen content of the red cells in a group of 47 individuals of Rh type $Rh_0(D)$ positive, rh′(C) negative by means of incomplete anti-$Rh_0(D)$ serum labeled with I^{131}. He found a bimodal distribution (Fig. 42). Family studies indicated that the persons with cells showing lower antigen content were heterozygous for $Rh_0(D)$ and that those with cells showing 1.6 times more $Rh_0(D)$ were homozygous.

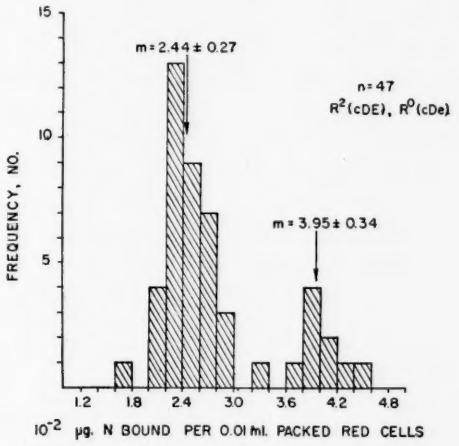


Fig. 42.—A genetic dosage effect on a red cell antigen. The group with the higher mean antigen level is considered to be homozygous and the other group heterozygous for the gene determining $Rh_0(D)$ antigen. (From Masouredis, S. P.: Science 131:1442, 1960; published by the American Association for the Advancement of Science.)

Individuals with no C, C^w, C^x, c, E, E^w, or e antigens in the Rh system have been encountered very rarely. The homozygote is indicated as D—/D—. Moore and colleagues found a new family (in Nova Scotia) in which 2 daughters from a consanguineous mating were of genotype D—/D—. Several other homozygotes and several heterozygotes were discovered in the family. The proband had erythroblastotic offspring.

Hemolytic disease of the newborn caused by anti-c antibodies was reported by Hiehle, Altamirano, and Kuhlman.

It was encouraging to find a reduction, however slight, in the complexity of the Rh system—Race, Sanger, and Lawler revoked a previously described Rh antigen, c^v. Using newer sera, they conclude c^vDE/cde is in fact CDE/cde.

Rosenfield and colleagues illustrated certain problems in Rh typing with experiences in a single Negro family.

Tate and others described 3 siblings, members of an inbred family of French extraction living in Louisiana, who were homozygous for a very unusual Rh complex, Dc—.

810. The MNS system. Jack and colleagues demonstrated blood group M_1, a subdivision of M comparable to A_1. In a small series of Caucasians and Negroes, they found the frequencies of the M_1 allele to be 0.13 and 0.03, respectively. Cleghorn reported data on gene frequencies in English blood donors.

Others: 811. The *Diego* factor has not been found in Caucasians and Negroes, only in Indians and Mongoloids. Yokoyama, Murakata, and Ueno found a lower frequency in northern Japan than in southern Japan. They suggested that the Diego factor is an Asiatic characteristic like groups B, Rh_0, kk, and Gm^a. Herman and Herman studied the Diego factor in Koreans. Kornstad found the Diego blood group antigen to be absent in Lapps.

Clarke, McConnell, and Sheppard concluded from sibling pair data that the amount of A, B, or H antigen secreted by an individual is in part inherited and that the genetic control is probably polygenic.

Bianco and colleagues contributed further to the understanding of the complex interrelationship of the *Lewis* and secretor characters. Levine reviewed recent observations on the Lewis system.

Rosenfield and associates described a Negro family in which there was present an allele bearing the antigen specificity of both Hu (*Hunter*) and He (*Henshaw*) as well as N and S (NS Hu He). Both Hu and He characters occur almost exclusively in Negroes. Hu is usually associated with Ns, and He usually with NS, in the MNS system. In the same family, the Js antigen recently (¶493) discovered by Giblett and Chase was identified and found to have segregated independently of the Lewis phenotype. Giblett had succeeded in showing the lack of linkage with eight other blood group systems. Only linkage with the Lutheran character remains to be studied.

812. Four families with the Swann antigen (Sw^a) have now been described (Cleghorn). They are apparently unrelated, one having come from Turkestan and the other three being socially and geographically widely separated in England. The frequency of the blood type in England is estimated to be about one in 6,000.

813. Rosenfield and colleagues described 3 cases of antibody to a very common red cell antigen, Ge. Two siblings of persons with antibody were found to lack the antigen. Among 11,500 persons tested, including Caucasians, Negroes, and Asiatics, the antigen was found to be present in all. There was no relation to systems ABO, MNSs, P, Rh, Kell, or Kidd, and the new antigen promises to be the charter member of a new system.

Miscellaneous.—

814. Imparato found chronic ascites and portal hypertension with a case of Gaucher's disease. Portacaval shunt relieved the ascites.

Crocker and Landing pointed out that the cytoplasm of Gaucher cells shows a strong histochemical reaction indicative of acid phosphatase, and acid phosphatase of the serum is usually elevated. A significant temporary decline in acid phosphatase of the serum occurs after splenectomy. The levels were not elevated in persons possibly heterozygous for a recessive gene (i.e., parents). (See also ¶515.)

Stein and Gardner studied the mean incorporation of C^{14}-labeled glucose and galactose in the microsome supernatant fraction of normal spleen (removed from a ruptured spleen in a boy involved in a sledding accident) and of spleen from a patient with Gaucher's disease. Both sugars were incorporated into the cerebroside of spleen with Gaucher's disease to a greater extent than in the normal person. After heating, glucose incorporation was slightly diminished in the diseased spleen and galactose incorporation much increased. They suggested that in formation of cerebroside, glucose is first added to sphingosine and fatty acid is then added; that in turn conversion of glucose cerebroside to galactose cerebroside is catalyzed by a heat-sensitive epimerase enzyme; that a defect in this enzyme might result in an accumulation of glucose cerebroside; that a defect in the catabolism of galactose cerebroside might account for those cases in which galactose cerebroside is found to accumulate.

Trams and Brady studied cerebroside formation in slices of splenic tissue from 4 patients with Gaucher's disease, using labeled glucose, galactose, and acetate as substrates. They concluded from comparisons with 2 cases of Niemann-Pick's disease and one of thrombocytopenic purpura that the biosynthesis of cerebrosides is not sufficiently elevated in Gaucher's disease to warrant the view that it is due to increased rate of sphingolipid formation.

XI. CARDIOVASCULAR SYSTEM

815. Phillips and Burch published a more extensive draft of their review of cardiovascular disease in white persons and Negroes (¶506). Genetic aspects were considered in a conference on methodology in the study of the epidemiologic aspects of hypertension and arteriosclerosis (Pollack and Krueger).

816. Hypertension. The question of the genetics of essential hypertension was further debated (see ¶507) by Oldham and colleagues and by Morrison and Morris, with rebuttal by Pickering, Miall, Fraser Roberts, and others. Cruz-Coke raised an objection to basing a conclusion on *systolic* pressure, which is so vulnerable to influence by other factors such as cardiac stroke volume and rigidity of the aorta. He pointed out that Morrison and Morris failed to find the bimodality in diastolic pressures. In an editorial, McKusick discussed the recent controversy of the monofactorial versus the polygenic nature of the heredity in essential hypertension.

Perera and Adler reported a deficiency of blood group A in Negro females with malignant hypertension. Thomas and Cohen found that smokers more often gave a history of parental hypertension than did persons who were not smokers.

Marshall found that in patients under 60 with cerebral infarction, blood pressures described a bimodal distribution. The higher mode was represented by those cases in which one or both parents had died under the age of 65.

In an ingeniously designed study, Humphries determined the frequency of hypertensive toxemia of pregnancy in the mothers of women who had hypertensive toxemia of pregnancy and compared the frequency with that in the mothers of women who were normotensive in pregnancy. More specifically, defining hypertensive toxemia as a diastolic pressure over 110 mm. Hg in a pregnant woman previously normotensive, he found 100 toxemic and 200 nontoxemic women who were in recent years delivered in the Johns Hopkins Hospital and who had themselves been born in the Johns Hopkins Hospital. For reason of the last fact, information was available on one pregnancy of the mother. The presence or absence of hypertension in that one pregnancy was the characteristic studied in the mothers. The results are shown in Table XVI.

Analysis of mean age, proportion of primiparas, proportion of Negroes, and other factors reveals no explanation for the observed difference. A genetic predisposition seems a likely explanation.

Phelan and Smirk studied genetically hypertensive rats, possibly comparable to the genetically hypertensive rabbits of Drury, Alexander, and their colleagues (Proc. Soc. Exper. Biol. & Med. 95:356, 1957). Both the right and left ventricles underwent hypertrophy. The rats had abnormally high heart rates, reminiscent of the finding by Levy and colleagues of tachycardia in persons who subsequently developed hypertension.

TABLE XVI

	NUMBER IN GROUP	FREQUENCY OF TOXEMIA	
		NUMBER	PER CENT
Mothers with toxemic daughters	100	28	28
Mothers with nontoxemic daughters	200	26	13

817. Pheochromocytoma. Carman and Brashear described a father, son, and daughter with pheochromocytoma. This is the tenth family with multiple cases (Fig. 43). Analysis of these ten families suggested that the condition is inherited as an autosomal dominant trait and that in the familial cases there is a strong tendency for the occurrence of pheochromocytomas at multiple sites. The mean age of the 25 definite patients in these ten families was 22 years at the time of diagnosis (range, 4 to 57 years).

Three members of a family reported by Cook and colleagues had pheochromocytomas arising in the organs of Zuckerkandl (paraganglionic chromaffin bodies adjacent to the aorta near the origin of the inferior mesenteric artery). In 2 of the cases there were malignant changes. Stigmata of neurofibromatosis

(¶507) were not present. Palmer described a patient with neurofibromatosis complicated by both neurofibromatosis and pheochromocytoma. Von Hippel-Lindau disease is another phacomatosis which is sometimes complicated by pheochromocytoma (Fig. 44).

Mařalka, Palečková, and Hradec found pheochromocytoma in 6 members of three generations. Two of the 6 patients had hibernoma (brown fat of tumorlike appearance).

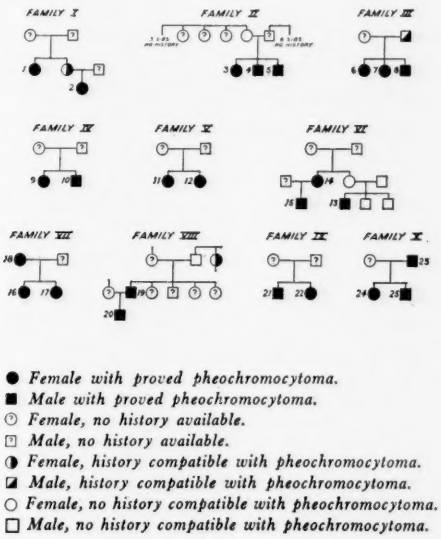


Fig. 43.—Pedigrees of ten families with pheochromocytoma. (From Carman, C. T., and Brashear, R. E.: New England J. Med. 263:619, 1960; published by the Massachusetts Medical Society.)

818. Atherosclerosis. Bjurulf did an autopsy study to correlate body build (skeletal, muscular, and fatty tissues) with atherosclerosis. He concluded that the grade of coronary atherosclerosis tends to vary with the amount of muscle tissue and with the size of fat cells but not with skeletal dimensions or with the number of fat cells. He had also concluded that the size of fat cells reflects dietary intake and other environmental factors, whereas the number of fat cells reflects genetic disposition.

819. Rheumatic fever. Clarke, McConnell, and Sheppard were unable to determine a significant excess of nonsecretors in patients with rheumatic carditis (see ¶509). They did, however, find a significant reduction in blood group O. There was no heterogeneity between these data and those of Glynn, Glynn, and Holborow (1959), who found a significant excess of nonsecretors and a nonsignificant deficiency of group O. On combination of the data from Liverpool and Taplow, there was found to be a significant increase in the frequency of the disease in persons who are not group O and who are nonsecretors. In their discussion,

Fig. 44.—Pheochromocytoma in von Hippel-Landau's syndrome. L. M. S. was 24 years old when she died of subarachnoid hemorrhage from rupture of hemangiomata of the medulla. (The patient had paroxysmal hypertension which may have contributed to the subarachnoid bleeding, and she was also pregnant near term at the time of death). A pheochromocytoma was discovered in the right adrenal gland.

A sister, M. M. M. (764463), now 36 years old, has von Hippel-Landau's syndrome manifested by angiomatosis of the left retina and signs of vascular malformations in the brain stem and cerebellum. An episode of paroxysmal hypertension occurred during preparation for diathermy of the retinal angiomata, but thorough investigations never succeeded in demonstrating pheochromocytoma.

The mother of these 2 women had long-standing impairment of vision and died of brain tumor. Two brothers of the maternal grandfather went blind.

(Slides courtesy of Dr. George Margolis, Professor of Pathology, Medical College of Virginia.)

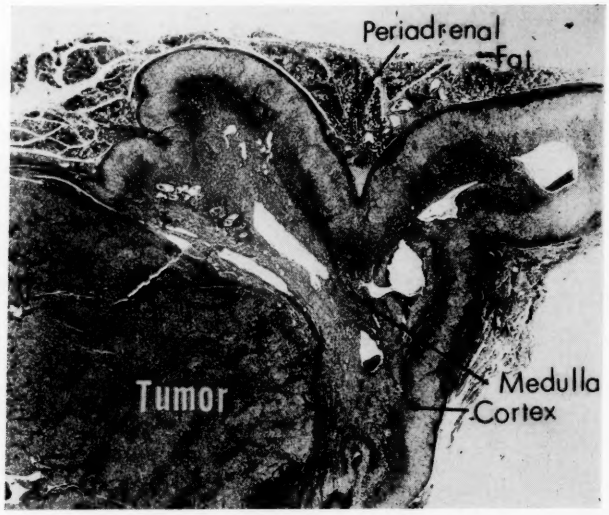


Fig. 44*A*.—The relation of the tumor to the medulla of the adrenal gland (×7, reduced 1/5).

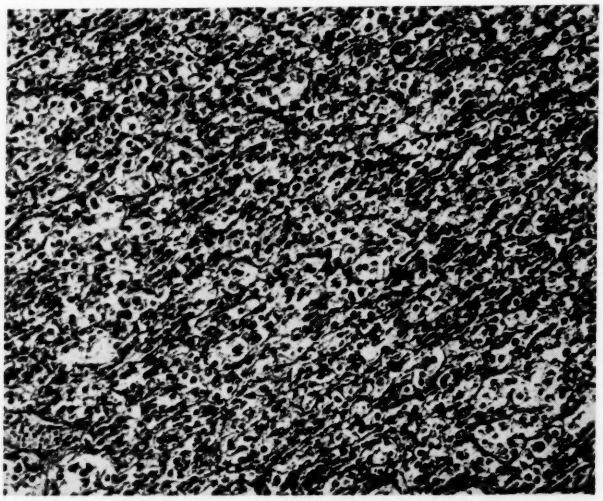


Fig. 44*B*.—The histologic of the tumor (×200, reduced 1/3).

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they point out that it will be of interest to know whether (1) water-soluble blood group substances in the media affect the virulence or growth of streptococci and (2) whether similar associations are demonstrable for uncomplicated streptococcal throat infections and acute nephritis.

Davies and Lazarov studied rheumatic fever in a communal settlement (kibbutz) in Israel. They found the prevalence of rheumatic heart disease to be two and one-half times greater in children of parents themselves affected than in controls seemingly exposed to the same environmental risks.

Congenital malformations of the heart and great vessels: 820. Winter and colleagues described *primary endocardial fibroelastosis* in 2 sisters. Zanker and Fisher described a brother and sister who died of endocardial fibroelastosis at the ages of 3 and 7 months, respectively. The experience is now sufficiently extensive to suggest that there is at least one form of the disease which is genetic and which is inherited as an autosomal recessive trait. A systematic investigation of the families of autopsy-proved cases is desirable.

Lynfield and colleagues studied 32 patients with endocardial fibroelastosis and suggested that two clinical categories exist: (1) those with left ventricular

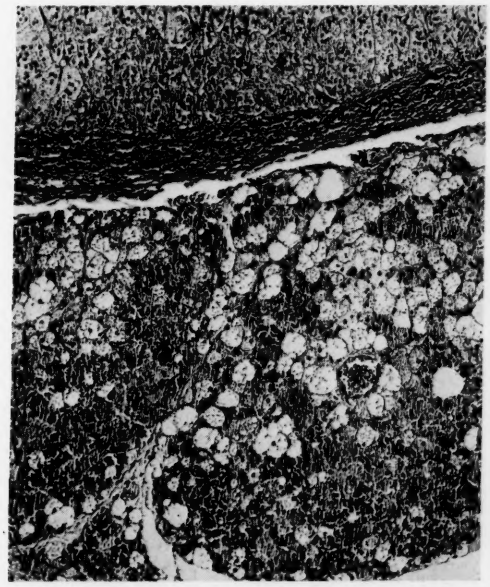


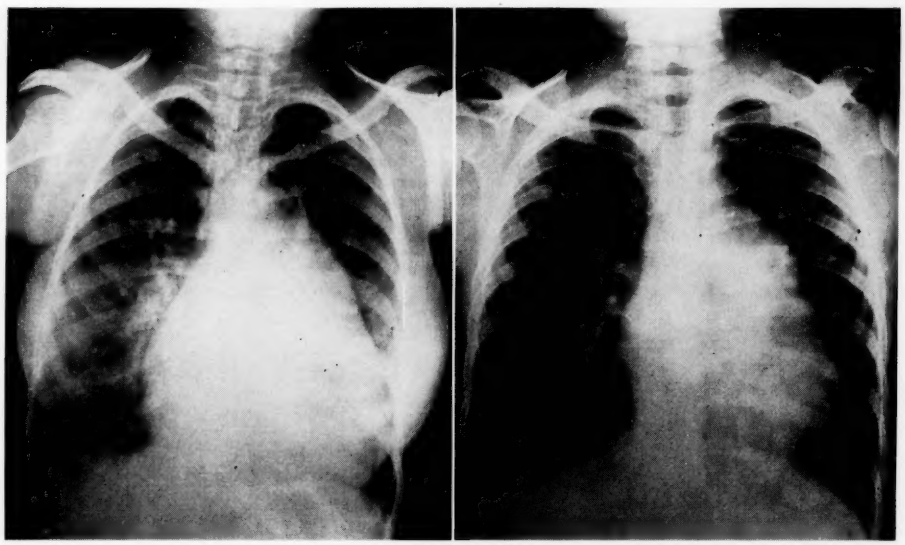
Fig. 44*C*.—The unusual appearance of the periadrenal fat, a characteristic of pheochromocytoma (×100, reduced 1/3).

hypertrophy, dilatation, and failure and (2) those with a left ventricle of normal or reduced size. In the second type, pulmonary hypertension and right ventricular hypertrophy are features. They believe the primary defect is in the myocardium, not the endocardium, and that the expression idiopathic cardiac hypertrophy

type I or type II with endocardial fibroelastosis serves a more appropriate designation.

Wilson and Clark described glycogen storage disease in 3 siblings, 2 of whom had endocardial fibroelastosis at autopsy. The picture of the disease has been described with the Hurler syndrome and with progressive muscular dystrophy (Levin and colleagues).

Fig. 45.—Negro mother and daughter with the Holt-Oram syndrome.



A. *B.*

Fig. 45*A* and 45*B*.—Both the mother (*A*) and the daughter (*B*), her only child, have typical radiographic changes of atrial septal defect. Both have electrocardiographic changes, specifically incomplete right bundle branch block pattern, consistent with that diagnosis. In the daughter, the diagnosis of atrial septal defect has been confirmed by cardiac catheterization.

Mehrizi and Oppenheimer described 2 unrelated patients with heart failure associated with unusual deposition of glycogen in the myocardium. One of the patients had endocardial fibroelastosis. The families of these patients should be investigated, especially since the histologic and clinical course was most like that of the brothers reported by Antopol and colleagues (1940).

Holmes, Houghton, and Woolf described a myopathy (affecting skeletal and cardiac muscle) occurring in adult life and having features suggestive of glycogen storage disease. Again a similarity to the condition described by Antopol (1940) was noted. In the family of their female patient, many, including 3 siblings, had died "in infancy or early adulthood" of pneumonia or heart disease. Autopsy revealed in the glomeruli and convoluted tubules of the kidney material with the tinctorial characteristics of mucopolysaccharide. Since the finding suggested that excess mucopolysaccharide was being excreted, the authors suggested that it be sought in the urine of persons with perplexing myopathy. They made interesting

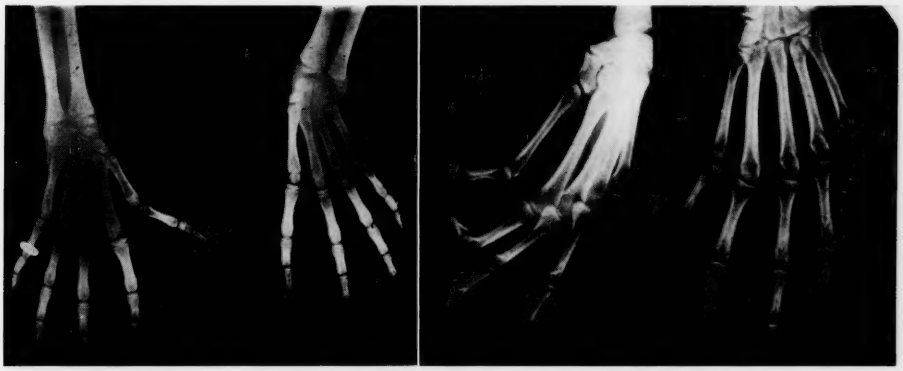
reference in passing to the basophilic degeneration of the myocardium which is observed in familial myoclonic epilepsy (Harriman and Millar, 1955).

Walther, Madoff, and Zinner described cardiomyopathy of unknown cause in 3 brothers under the age of 10 years. Two other male siblings were normal. The parents were not related. Two of the siblings died suddenly at the age of 8 years. Massive hypertrophy of the left ventricle with increased interstitial connective tissue was revealed by autopsy.

Beasley described idiopathic myocardial disease in 2 brothers and a sister. Death occurred at ages 5, 7, and 34 years, respectively.

821. Hollman and colleagues found 9 members of two generations of a family affected with *obstructive myocardiopathy* (asymmetric hypertrophy). It behaved as an autosomal dominant trait. Braunwald and colleagues described idiopathic hypertrophic subaortic stenosis. They reviewed the familial cases in the literature. In their series of 14 patients, 3 were siblings and they observed an affected mother and son. In the latter family, 2 sisters of the mother were probably also affected. Brent and colleagues performed a large study of familial muscular subaortic stenosis.

Reynolds and colleagues described *congenital valvular aortic stenosis* in male siblings. Sudden death, despite the absence of electrocardiographic features of much left ventricular hypertrophy, was a feature. Brent and colleagues described two apparently unrelated families with multiple cases of muscular subaortic stenosis, which seemed to be transmitted as an autosomal dominant trait. Nine were affected in three generations of one family, 7 in two generations of the second. A characteristic of the central aortic pulse was a rapid initial systolic upstroke and of the left ventricular pulse a deflection on upstroke, caused perhaps by



C. *D.*

Fig. 45*C* and 45*D*.—Both have an anomaly of the bones of the wrist and hands. The daughter (*C*) has no thumb on the left hand and a marked anomaly of the wrist, with only four carpal bones irregular in contour and a fifth tiny bone between the hamate and capitate. On the right hand there are five digits, but all resemble fingers, none a thumb; all, including the "thumb," have three phalanges.

The mother (*D*) also has anomalous thumbs and anomalies of the carpal bones. The orientation of the thumb resembles that of a finger. The joint spaces between the navicular and multangular bones are bilaterally narrow and irregular. On the left there is a small extra bone between the hamate and capitate. Deformity of the wrist bones was present in the patients of Oram and Holt also.

initially less obstructed ejection followed by increased outflow obstruction from active contraction of the hypertrophied muscle responsible for the narrowing below the aortic valve.

822. Holt and Oram observed *atrial septal defect* and congenital anomaly of the hands in four generations. The skeletal anomaly was described as a "congenital anomaly of the thumbs which lay in the same plane as the fingers, their terminal phalanges being curved inwards." There was also deformity of the carpal bones. We have observed the same association, which therefore seems to be a true hereditary syndrome, in mother and daughter (Fig. 45). Should it be called atriodigital dysplasia or the Holt-Oram syndrome?

Polani and Campbell made inquiry into the family history of 261 patients with patent ductus arteriosus (PDA). Those with other malformations of the heart (about one-tenth of the total) were excluded. Six per cent of patients with PDA had noncardiac malformation. Two per cent of siblings had cardiac malformation, usually PDA. There was no good evidence of an increase in the parents or offspring of probands. First cousin marriages occurred in the parents of 1.6 per cent of probands. There were, as usual, more females with PDA than males. More girls with PDA were born during the second half of the year, especially from August to October; boys did not differ from the expected, these findings being consistent with those of Record and McKeown (1953).

Alvarez-Borja reported 2 cases of the Ellis-van Creveld syndrome (¶510).

823. Neill and colleagues described a father and daughter with hypoplastic right lung with systemic arterial supply and venous drainage. They referred to the disorder as the "scimitar syndrome" because of the radiographic appearance created by the anomalous vein draining the right lower lung and connecting with the inferior vena cava. The father was asymptomatic but had been rejected for military service because his heart was said to lie on the right side. The hypoplastic right lung and increased right-sided venous return—mainly the former—are responsible for a prominence of the right heart border suggesting dextrocardia. The daughter had severe pulmonary hypertension, frequent respiratory infections, and marked hypoplasia of the right lung with dextroposition of the heart. Stimulated by the observations cited above, we have studied 8 children of the patient with "scimitar syndrome" described by McKusick and Cooley (1955). No abnormality was detected.

Berg, Crome, and France discussed congenital heart disease in *Mongolism.*

824. Miscellaneous. Thomas, Harris, and Lassiter analyzed the electrocardiograms of 320 healthy Negroes varying in age from 20 to 40 years. Only 3 (0.9 per cent) had inverted T waves as far to the left as V_3 in the precordial leads. Of these, 2 were women. Thus no evidence of an increased incidence of juvenile pattern in Negroes was discovered. Elevation of the ST segment in the precordial leads of 2 mm. or more was found in 89 men (27 per cent) but in only one woman.

Wallgren and Agorio diagnosed congenital complete heart block antenatally n 3 siblings. Two who had a ventricular rate less than 46 per minute died at less

than 10 days of age. A third, with a pulse rate over 64 per minute, survived. No comment about parental consanguinity was made.

Bacos, Eagan, and Organi presented a family in which 9 members of three generations exhibited nodal rhythm with bradycardia and tended to develop paroxysms of atrial fibrillation as they entered the fourth decade of life.

Saunders described a method alleged to effect permanent control of nosebleed in patients with *hereditary hemorrhagic telangiectasia:* septal dermoplasty, grafting of skin over the anterior third of the nasal septum bilaterally.

XII. CONNECTIVE TISSUE

Gene-Determined Disorders.—

825. Marfan syndrome. Case reports were provided by Zaidi, by Martin and Cowan, by Knight, Clark, and Terry, by Kohn and Strauss, by Jain and Sepaha, by Consul, Kutshrestha, and Kasliwal, by Liboro and colleagues, by Tatoń, and by others.

Capotorti, Gaddini de Benedetti, and Rizzo studied an Italian family with 16 affected members in three generations. The family contained an instance, the first known, of a marriage between 2 affected persons who were first cousins. Of 9 children, 4 were affected, one was normal, 3 died in infancy, and one was stillborn. Two of the 4 children showed the manifestations in more severe form than did any other patients in the pedigree.

Sinclair, Kitchin, and Turner reported on 40 patients with the Marfan syndrome distributed in eighteen families. They suggested the metacarpal index as an objective indication of arachnodactyly. In the right hand x-ray, the length of the second, third, fourth, and fifth metacarpals was measured in millimeters. At the exact midpoint of each shaft, the breadth was also measured in millimeters, and this value was divided into the length. The resulting figures, for each of the four metacarpals, were averaged. The metacarpal index is, then, the average ratio of length to breadth of metacarpals II to V. The results in 20 patients and in 100 normal subjects are given. There was no overlap of the two distributions. Since skeletal features alone were accepted in the diagnosis, some circular reasoning may have entered this study. The frequency distribution is distinctly peculiar; it suggests a continuous distribution with one class missing (Fig. 46).

Parish, Calnan, and Lawrence, in separate communications to the Royal Society of Medicine, discussed genetic factors in diseases of connective tissue. Points of particular interest will be noted. Parish, using Sinclair's index of arachnodactyly, reported some normal control data and indicated overlap between the normal and Marfan syndrome groups. He suggested that arachnodactyly with mandibulofacial dysostosis, particularly receding lower jaw, is a syndrome separate from Marfan's and properly called Achard's syndrome. In the patient he described, a 40-year-old woman, joint laxity was confined to hands and feet.

By gonioscopy, von Noorden and Schultz described typical changes in the angle of the anterior chamber of the eye. These findings may be useful in

determining the presence of the Marfan syndrome in members of families with one or more other less equivocal cases. The findings are not unique to the Marfan syndrome, as indicated in ¶848. Burian described a case of bilateral glaucoma in the Marfan syndrome.

Steinberg described 5 more cases of dilatation of the aortic sinuses in the Marfan syndrome. One of the patients is of interest relative to Loughbridge's report. The 9-year-old child had mental deficiency, spider fingers and toes, a diastolic murmur, and a much dilated ascending aorta. The right kidney was atrophic. The left had advanced hydronephrosis and hydroureter from obstruction at the bladder neck. At autopsy, patent ductus arteriosus and a bicuspid aortic valve were demonstrated. The family history was apparently negative, and the lenses were not described as subluxated. In a second patient, a Hufnagel valve placed in the usual site in the first part of the descending aorta tore out after about one year. The change in the aorta at the prosthesis was probably similar to that which develops in stethoscope tubing at the junction with metal parts. The experience may be further evidence of a "wearing-out" nature of the progressive change which occurs in the ascending aorta in this disease.

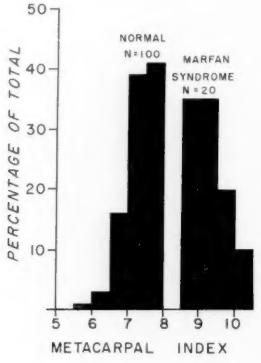


Fig. 46.—Metacarpal index in the Marfan syndrome. (Data of Sinclair, R. J. G., Kitchin, A. H., and Turner, R. W. D.: Quart. J. Med. 29:19, 1960; published by the Oxford University Press.)

Ross and Gerbode described a 15-year-old white girl with typical features, both ocular and skeletal, of the Marfan syndrome. An unusual type of ventricular septal defect was repaired by open heart surgery. There was an aneurysm of the membranous septum bulging into the outflow tract of the right ventricle and displaying a fenestration (Fig. 47). It is attractive to suppose that the weakness of the membranous septum was part of the generalized disorder of connective tissue and that stress-fatigue was responsible for the fenestration. The murmur heard at an early age may have been produced by partial obstruction of the outflow tract by the aneurysm of the membranous septum, and the rupture of the aneurysm may have occurred sometime in the years since birth and not have been congenital.

McKeown described a 21-year-old white man with arachnodactyly but "no other stigmata of Marfan's syndrome." The patient died from myocardial infarction resulting from dissection limited to the right coronary artery.

Kachele described an instructive patient with the Marfan syndrome and striae of the skin in the pectoral and anterior deltoid areas. He suggested that this finding supports the view that the disease is an abiotrophy of elastic tissue.

Bacchus (see ¶178) studied further serum mucoprotein (now more generally called seromucoids) in the Marfan syndrome and added observations on acid mucopolysaccharides. He again concluded that the serum mucoproteins are abnormally low whereas acid mucopolysaccharides are abnormally high. Lehmann found no abnormality of serum mucoproteins or urinary amino acids in the numerous affected members of a family.

Tjio, Puck, and Robinson described one chromosome with giant satellites in each of 2 patients designated as having familial Marfan's disease. They stated that "while the present data do not prove the given abnormalities to be the underlying cause of Marfan's syndrome, a relationship is definitely suggested." This fascinating observation must be pursued in clinically well-studied cases.

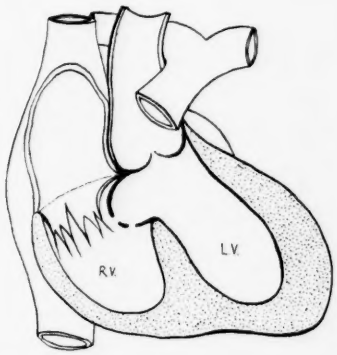


Fig. 47.—Ruptured aneurysm of the membranous interventricular septum in the Marfan syndrome. (From Ross, J. K., and Gerbode, F.: J. Thoracic Surg. 39:746, 1960.)

We have observed ventricular septal defect, confirmed by cardiac catheterization, in a single case of the Marfan syndrome (G. H., 815634). Whether the mechanism of the defect was as outlined here is, of course, not known.

The cytologic demonstrations were convincing. However, for several reasons, it seems very unlikely (McKusick) that there is a gross and specific chromosomal aberration of this type in the Marfan syndrome:

1. Most importantly, it is by no means certain that the 2 patients with satellite peculiarities had the true Marfan syndrome. In neither was ectopia lentis noted. One had tricuspid atresia and atrial and ventricular septal defects—a complex of cardiac malformations quite unknown in the Marfan syndrome. The other, an 18-month-old infant, had only skeletal features, which are notoriously unreliable as the sole basis of the diagnosis. Although extensive pedigrees of the

2 patients are shown, in one "the genealogy was established from the patient's hospital record" and "no other members of this patient's family are available for study." In the second family, the pedigree chart was apparently assembled only by hearsay "from questioning of members of the patient's family, who have been very cooperative." No indication is provided that any of the family members said to be affected had ectopia lentis or aneurysm of the aorta with aortic regurgitation, less disputable manifestations of the Marfan syndrome. It is stated that "this condition is a relatively poorly characterized clinical situation." On the contrary, its nosography has advanced to a quite high plane. The clinical picture is admittedly varied but is no more variable than, for example, those produced by many specific microorganisms.

2. In the same report, the authors describe a case of obviously bona fide Marfan syndrome with ectopia lentis, skeletal changes, and a heart lesion. That the case was sporadic is no necessary indication that it was basically different from familial cases of the true syndrome. In this one acceptable case of the Marfan syndrome, there was no satellite peculiarity.

3. In the 2 patients with satellite peculiarities, chromosome 21 was affected in one and chromosome 18 in the other. Although heterogeneity may well exist in the Marfan category, this lack of consistency weakens the hypothesis of a specific relationship.

4. Such giant satellites are occasionally seen in patients without stigmata of the Marfan syndrome.

5. Ford and also Böök's group (cited by Ford) have examined the chromosomes in patients with the Marfan syndrome without detecting this abnormality, which to be sure could perhaps have been overlooked.

As stated above, the cytologic observations can scarcely be questioned. Furthermore, in the 2 patients, the peculiarity described may bear a causal relationship to the malformations present in each. However, it is doubtful that the satellite peculiarity is the specific underlying cause of the Marfan syndrome.

Muller, Dammann, and Warren described surgical procedures performed in 3 patients with the Marfan syndrome with severe aortic involvement. Marlier performed the Hufnagel procedure in one case.

Loughridge described renal involvement in 8 patients she considered to have the Marfan syndrome. One (case 4) undoubtedly had the true Marfan syndrome; ectopia of the left kidney with pyelonephritis and hypertension was present. In some of the others, relatives were of gangly habitus, but no unequivocal manifestations such as ectopia lentis or aortic aneurysm were described. At autopsy in one case, the aorta was thought to be hypoplastic, but no dissection or cystic medial change was described. Apparently no slit lamp search for minor changes in the suspensory ligament of the lens was made. Some or even all these cases may indeed be examples of the Marfan syndrome, but without more evidence than "spider" fingers, a "droopy" appearance, and muscular hypotonia, the Scottish verdict of "not proved" is necessary.

Reeve, Silver, and Ferrier described a girl who died at the age of 3½ months and who had features of both the Marfan syndrome and of arthrogryposis (amyoplasia congenita). Indications of the Marfan syndrome included dolichocephaly,

high-arched palate, dislocation of the right lens, long and thin extremities, and, at autopsy, marked dilatation of the aorta. (Complete autopsy was not available.) There were multiple joint abnormalities: thumbs and elbows fixed in flexion, inability to abduct arms, dislocation and adduction of both hips, and talipes calcaneus. Muscular development was strikingly deficient. No other member of the family had evidences of either abnormality. The occurrence together in this case may have been coincidence. There is little evidence of a genetic basis of arthrogryposis (¶'s 263, 905). However, the authors refer to another case of the combined syndrome.

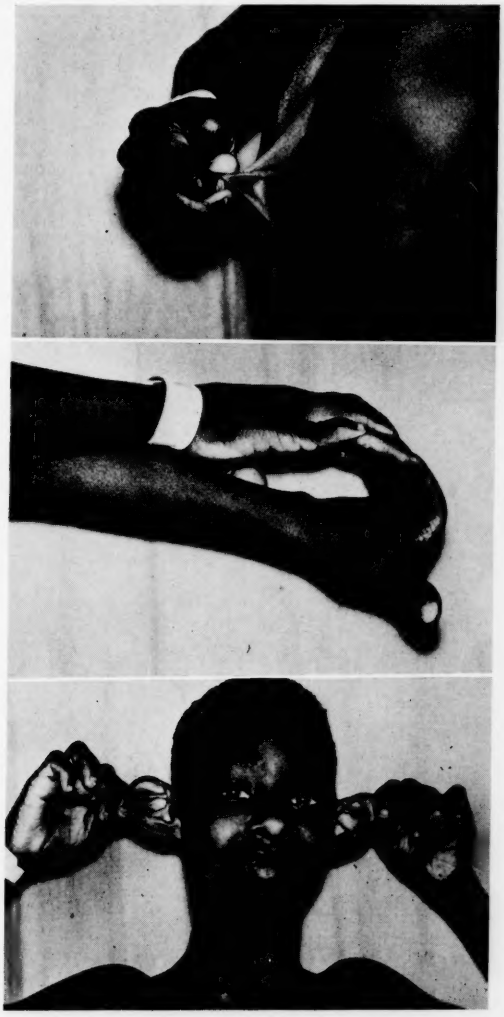


Fig. 48.—The Ehlers-Danlos syndrome. Abnormal extensibility of the skin (*A*), joints (*B*), and ears (*C*) are demonstrated in a 12-year-old boy. Fragility and bruisability of the skin are not present. Rather few instances of this disorder have been reported in Negroes. (Courtesy of Dr. Glenn R. Stoutt, Louisville, Ky.)

826. Ehlers-Danlos syndrome (Figs. 48 and 49). Case reports were given by Ermert.

In a family with the Ehlers-Danlos syndrome transmitted through four generations, a mother and daughter studied by Lisker, Noguerón, and Sánchez-Medal showed plasma thromboplastin component (Christmas factor, factor IX) deficiency.

Lapayowker described the x-ray findings, especially that of multiple small, subcutaneous nodular calcific densities, especially in lower extremities.

Mories reported the fatal case of a 15-year-old boy with the Ehlers-Danlos syndrome. Following a fall from his bicycle, the boy developed bleeding in the groin area. All measures to halt the bleeding failed—largely because the tissues were so friable.

827. Osteogenesis imperfecta. Mussio made an in utero diagnosis of osteogenesis imperfecta congenita. Sarma described a case in India. He commented on the jigsaw puzzle pattern which results from the multiple Wormian bones and pointed out that the diagnosis can be made intrapartum by palpation of the characteristic skull. However, we have the impression that breach presentation occurs with high frequency when the infant is affected by osteogenesis imperfecta.

Over a 10 year period, Bergman studied the teeth of a boy with multiple fractures. The sclerae were not unusually blue.

Orthopedic treatment was discussed by Murray and Young, by Yeoman, and by others.

Heys, Blattner, and Robinson described the teeth in five families with osteogenesis imperfecta known in two to four generations, five families with odonto-

Fig. 49.—The Ehlers-Danlos syndrome. R. A. (911928), age 60 years, has all the typical features. He subsequently succumbed to metastatic squamous cell carcinoma of the nasopharynx. No other member of his family is affected. Unusual facility in touching the tip of the nose with the tip of the tongue is frequently present in the Ehlers-Danlos syndrome. Note the scarring of the forehead.

genesis imperfecta known in two to six generations, and eight families with both conditions known in two to six generations. They subscribed to the view that "the two clinical entities are manifestations of the same basic pathologic state." However, in those families in which multiple members of many generations have only odontogenesis imperfecta, one would suspect that a different gene is involved than in those families with involvement of the skeleton as well.

Awwaad and Reda described 2 cases of congenital osteogenesis imperfecta in one sibship. Fig. 50 refers to a similar family. Only one was studied by the authors, but the parents described a similar clinical condition in a second sibling who died at the age of 6 months. The parents were said to be clinically normal but were related—the precise nature of the consanguinity was not indicated. Recessive inheritance is suggested by the description, although with reduced penetrance of a dominant trait, occasional families of this type are to be expected. Yet other hypothetically possible explanations are "delayed mutation" and gonadal mosaicism.

Three of 5 adult siblings had basilar impression and osteogenesis imperfecta (Hurwitz and McSwiney). Wormian bones and dentinogenesis imperfecta were present but not blue sclerae. The father was also affected. The authors refer to the finding of multiple Wormian bones in four of seven skulls of members of a family found in an archeologic excavation at Lanhill Barrow (Keiller and Piggott, Proc. Prehistoric Soc. 4:148, 1938). It is clear from the original report that the family was not affected by osteogenesis imperfecta or cleidocranial dysostosis (two conditions associated with multiple Wormian bones) but rather had isolated Wormian bones as an anatomic variation which was probably inherited.

Keats and Anast described a family with osteogenesis imperfecta and several instructive features: (1) circumscribed rarefaction by x-ray, (2) transmission through at least three generations, with 2 and possibly 3 cases of the congenital form of the disease in the third generation, and (3) an apparent "skipped generation." In the first generation, a man apparently had his first fracture at age 8 years. He grew to be only 4 feet tall and used crutches all his adult life. His son (the apparently "skipped generation") was seemingly in good health and was 5 feet 10 inches tall. However, x-rays showed circumscribed bone rarefaction.

In cats, hereditary osteogenesis imperfecta has been thought to occur. Scott demonstrated that on certain diets, kittens are very susceptible to calcium depletion and that the symptomatology is precisely that seen in the described instances of osteogenesis imperfecta. As outlined by Scott, the cat has a number of peculiarities of metabolism and of nutritional requirements. Although some cats may be more susceptible to calcium depletion than others, it is unlikely that there is, in cats, a hereditary disorder of connective tissue analogous to the disease in man.

828. Pseudoxanthoma elasticum. Cases were described by Berlyne, by Schuermann and Woeber, and by others.

Calnan referred to a personal communication from Marten: A patient with pseudoxanthoma elasticum had pulmonary vascular changes like those described previously at other sites such as the gastrointestinal tract. Lobectomy had been

performed for hemoptysis. In 2 children with gastrointestinal bleeding, the skin seemed normal to inspection; histologically, however, minor but definite changes were demonstrated in the skin of the neck and axilla. (See Fig. 51.)

See ¶793 for a discussion of fundus changes (angioid streaks) and arterial changes, like those of pseudoxanthoma elasticum, in sickle cell disease.

Loewi, Glynn, and Dorling reported studies on the nature of degeneration in collagen. They were interested in particular in the altered collagen associated with basal cell carcinoma, but the same considerations or similar ones probably apply to other situations, possibly including pseudoxanthoma elasticum. To the altered collagen they prefer to apply Unna's term, collastin. Collastin stains like elastin with elastic tissue stains. Stains for tyrosine distinguish collastin from elastin. Elastase digests both collastin and elastin. Collagenase digests only collagen. Trypsin has no effect on any of the three. In the collagen extracted from

Fig. 50.—Two cases of osteogenesis imperfecta congenita in offspring of ostensibly normal parents. Shown here is the typical clinical and radiologic appearance of congenital osteogenesis imperfecta: micromelia and multiple fractures are shown in the newborn views (*A* and *B*) and hydrocephalus, which developed later, is shown in *C*, a view at age 10 months. The child died at 13 months. A male sibling with identical changes confirmed by x-rays and autopsy died at the age of 2 days. Another sibling, age 8 years, is normal.

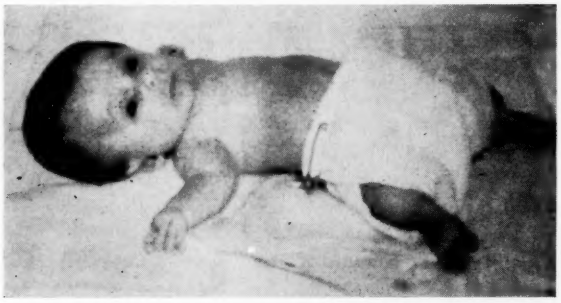


Fig. 50*A*.—Clinical view of the newborn child with micromelia and multiple fractures.

ox hide and in the collagen of tissue sections, these workers could produce fibers with properties of collastin: orcein positivity, elastase sensitivity, and collagenase resistance. Acetylation was the process used for extracted collagen; heating or treatment with salicylate was used for tissue sections.

829. The Hurler syndrome. Vanace, Friedman, and Wagner described advanced mitral stenosis in an affected boy who died at the age of 5½ years. No clouding of the cornea was noted, but slit lamp examination was not done. Cases were described by Hienz, by Guicheney, and by others.

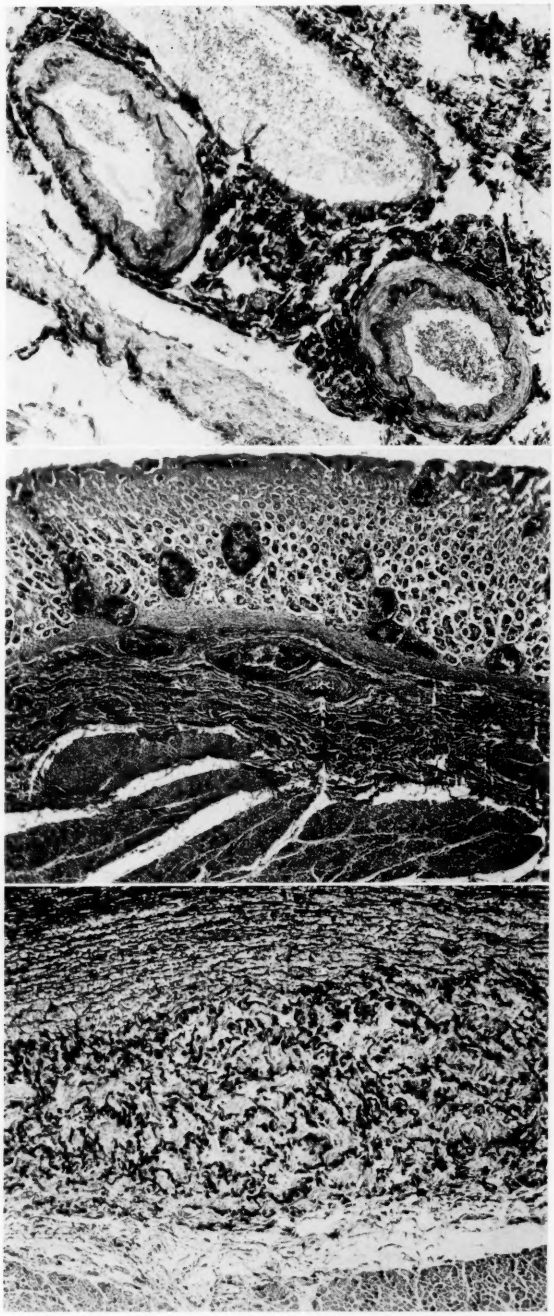
Jermain, Rohn, and Bond studied the blood and bone marrow in 12 cases of the Hurler syndrome, including a case in a Negro. In all, the macrophages in the marrow showed cytoplasmic inclusions which histochemically could be shown to be, at least in large part, mucopolysaccharide. Only one patient showed the Alder phenomenon—inclusions in the circulating white blood cells. This

Fig. 50*B*.—Roentgenologic view of the multiple fractures and micromelia.

individual also had inclusions in the lymphocytes and polymorphonuclear series of the bone marrow. The macrophagic inclusions appeared to be an early development. Asymptomatic parents and siblings were also studied, but with negative results.

Gorlin, Chaudhry, and Kelln emphasized that limitation of joint motion involves the temporomandibular joints. They used the unfortunate and clearly inappropriate designation lipochondrodystrophy.

Fig. 50*C*.—Hydrocephalus.



Figs. 51*A*, 51*B*, and 51*C*.—*A*, Vessels in wall of intestine (elastica van Gieson ×200; reduced 1/3). *B*, Stomach (hematoxylin and eosin ×60; reduced 1/3). *C*, Endocardium of right atrium (EVG ×150; reduced 1/3).

Fig. 51*D*.—Endocardium of right atrium (EVG ×60; reduced 1/3).

Fig. 51.—Pseudoxanthoma elasticum. N. C. was 13 years old at the time of death from gastrointestinal hemorrhage. Vomiting of blood or passing of blood in the stools had occurred repeatedly in the previous 6½ years, necessitating nine hospital admissions. Death occurred in 1945. The diagnosis was always in doubt clinically. At autopsy, too, there was arrival at no satisfactory diagnosis. The diagnosis of pseudoxanthoma elasticum was made in a brother, now 38 years old, on the basis of typical skin and eye changes and a history of gastrointestinal bleeding on one occasion, at the age of 15 years. In retrospect, in the proband (N. C.), on a hospital admission 4 years before death, it was noted that "over the cervical region is a raised pebbly eruption." Later it was recorded that "over the neck, chest, abdomen, and a small amount over the flexor surfaces of the arm there were elevated, small white papules some discrete, others confluent, which appeared like scar tissue. This is similar to some skin conditions which she had previously." On one occasion, the diagnosis of pseudoxanthoma elasticum was suggested by a dermatologist, along with other possibilities, but the total picture was not put together. An ophthalmologist commented as follows: "The eye grounds are essentially negative. Over a broad area temporally from the fovea in both eyes, there is a peculiar light brown mottling. The patient's brother is said to have this too and also the same sort of bleeding."

Histologic studies revealed astonishing focal or segmental vascular changes, especially in the stomach and small intestine, but also in many other organs, including heart, pancreas, kidney, and to some extent the brain. The changes were like those illustrated by Carlborg (¶521). In some vessels, there was fragmentation of the elastica and a deposit of collagenous material between it and the lumen, as well as loss of muscle (*A*). In the walls of some vessels, there was material which in part stained brilliantly red with picro-Mallory dye like "fibrinoid." Mucosal vessels in the stomach and intestine were widely dilated and exceedingly thin walled (*B*). The wall of the atrium showed dense "elastosis" of the endocardium (*C* and *D*). (Courtesy of Dr. Averill A. Leibow, Professor of Pathology, Yale University School of Medicine.)

The skin lesions were discussed by Levin.

Berry and Spinanger described a urinary spot test useful in the study of Hurler's syndrome. The test consists of toluidine blue O staining of urine dried on filter paper, for demonstration of mucopolysaccharide.

Turman used the disease trait snorter dwarfism of Hereford cattle as an illustration of the methods that can be used to eliminate an undesirable gene from livestock. This condition is inherited as an autosomal recessive trait. Lorincz has studied the clinical and biochemical features of the disease in cattle.

830. Others. Smith and Waisman reported 3 members of a family with *osteopoikilosis* ("spotted bones") and the skin lesions which are associated. The histologic changes in the skin lesions, which were termed "connective tissue nevi," consisted of splinters and skeins of elastic tissue in the upper cutis, variable thickness of individual fibrils, nodulation of fibrils, and amorphous flakes.

Feinberg wrote about congenital mesodermal dysmorphodystrophy (brachymorphic type), his cumbersome designation for the *Weil-Marchesani syndrome.* Two affected sisters were described. Brachycephaly, short stature, and brachydactyly were skeletal features. The eyeballs were small and sunken. Both sisters had auscultatory and radiographic signs that were typical of patent ductus arteriosus.

Jacobson, Rifkin, and Zucker-Franklin reported 9 cases of the *Werner syndrome* (6 with autopsy) and reviewed the literature. Field and Louke commented on the presence of diabetes mellitus in a majority of cases of Werner's syndrome. Features are mildness, absence of ketosis, relative insulin insensitivity, and tendency of the fasting blood sugar to be normal. They speculated that the hyperglycemia might be related to an inability to metabolize dietary glucose and store it as fat. A deficiency of subcutaneous fat and deficiency of muscle mass characterize the Werner syndrome.

In a 39-year-old Persian Jew, the offspring of first cousins, Valero and Gellei observed, in addition to the well-recognized manifestations of Werner's syndrome, retinitis pigmentosa, arteriosclerotic occlusion of the right renal artery, and hypertension. Retinitis pigmentosa was described in a case that had been previously reported.

831. Miscellaneous considerations. The annotated bibliography of collagen research in chemistry, technology, and medicine prepared by the Research Division of Ethicon, Inc., should prove useful (Martin).

From analogy with the hemoglobinopathies, it is likely that one or more of the heritable disorders of connective tissue, e.g., osteogenesis imperfecta or the Ehlers-Danlos syndrome, will be found to have their basis in a highly pinpointed amino acid substitution. It is now firmly established that there is a discrete monomeric unit of collagen, the tropocollagen macromolecule, which is essentially a rigid rod about 14 × 2,800 Å in dimension with a molecular weight of about 360,000. On the basis of x-ray diffraction patterns, Rich and Crick have proposed a three chain helical configuration. Hodge and Schmitt studied "the charge profile of the tropocollagen molecule and the packing arrangement in native type collagen fibrils." Hodge and co-workers performed two dimensional paper chromatography of acid hydrolyzates of a fraction derived from collagen by enzymatic digestion.

Allgower and Hulliger presented evidence that mononuclear blood cells cultured from the buffy coat differentiate in vitro into fibroblasts. Specifically, they demonstrated hydroxyproline production by these cells. They used rabbit blood for initial culture. The implications in wound healing were emphasized by the authors. The usefulness of blood cultures in study of heritable disorders of connective tissue may be indicated.

Gene-Conditioned Disorders.—

832. Osteoarthrosis. Lawrence called attention to the occurrence of coxarthrosis in three generations, as reported by Böni in 1959. In the fourth generation, 2 persons had a troughlike defect in the head of the femora. This was presumably the inherited anomaly which predisposed to precocious coxarthrosis. In a familial study of coxarthrosis in Leigh and Wensleydale, Lawrence found a familial aggregation for osteoarthrosis which could not be accounted for on the basis of family similarities in occupation.

833. Fudenberg, German, and Kunkel studied relatives of 13 patients with congenital *agammaglobulinemia* and of 10 with "acquired agammaglobulinemia." Hypergammaglobulinemia was found frequently in both groups of relatives. Of parents and siblings of patients with acquired agammaglobulinemia, 46 per cent had rheumatoid factor, whereas 5 per cent of persons in control families showed rheumatoid factor ($p < 0.001$). Antinuclear (lupus) factors were present in relatives of 2 patients with acquired cases. In the congenital form, there was no increase in the frequency of rheumatoid factor in relatives.

Two instances of the familial occurrence of *systemic lupus erythematosus* were reported by Marlow, Peabody, and Nickel: 2 sisters of Italian extraction and a mother and daughter of Mexican background.

Pollak, Mandema, and Kark found positive results of tests for serum antinuclear factors in 19 of 36 first degree relatives and 5 of 14 second degree relatives of patients with systemic lupus erythematosus. In none of 40 healthy persons and in only one of 50 patients with diseases "unrelated to SLE" was a positive test result observed. The workers concluded that there may be in lupus patients a "hereditary abnormality in the homeostasis of the antibody-producing system." Data on the difference in "normal" level of γ globulin in Caucasians and Negroes were also presented.

Seip demonstrated pancytopenia in a mother with systemic lupus erythematosus and in her male newborn infant. Placental transfer of autoimmune substances was postulated. Obviously not strictly genetic, this type of mechanism must be kept in mind in evaluation of familial aggregation.

Lawrence pointed out that further analysis of the familial aggregation in *rheumatoid arthritis* suggests that at least two genetic varieties are involved: When the families of seropositive probands were studied, the frequency of seropositivity (for the sheep cell agglutination test) was greater than in controls regardless of whether clinical rheumatoid arthritis was present or not. In the families of seronegative patients with rheumatoid arthritis, clinical disease showed an increased frequency but seropositivity did not. The fact that spouses showed no increase in clinical, serologic, or radiologic evidence of the disease speaks for a genetic basis of the familial aggregation. (Unfortunately, these workers studied the spouses of only 17 subjects. A larger series is desirable.)

Lawrence made the following statement: "Since clinical disease is two-and-a-half times as common in females as in males, it may be considered whether one gene [for rheumatoid arthritis] is inherited as a sex-linked dominant on the X chromosome."

Denko and Bergenstal reported on 14 women and 2 men with *Sjögren's syndrome*, or the sicca syndrome. The frequency of arthritis in the family was impressive: patient 3—father; patient 4—mother and sister (dry mouth as well); patient 5—mother; patient 6—aunt; patient 10—mother; patient 11—mother; patient 13—mother and uncle.

Posner described a case of the rheumatoid pneumoconiosis *syndrome of Caplan* in a maker of grinding wheels.

Kornstad described two families in which only females were affected by *ankylosing spondylitis*. Genetic linkage with blood groups was sought. Moesmann described two pairs of monozygotic twins, one pair concordant and the other discordant for ankylosing spondylitis.

A general review of hereditary diseases of connective tissue was given by McKusick.

XIII. EAR

834. Everberg made a study of unilateral deafness in 122 children and adolescents, concluding that in 25 to 35 per cent the deafness has a hereditary basis. Mohr and Mageröy described a sex-linked recessive variety of progressive deafness. Both studies concerned deafness of nerve type.

835. DiGeorge, Olmsted, and Harley reported a series of cases of the Waardenburg syndrome (¶528), including the first cases in the Negro. The white forelock and depigmentation elsewhere are especially dramatic (e.g., their Fig. 20) in the Negro. They estimated that the Waardenburg syndrome accounts for 2 per cent of congenital deafness.

836. Deraemaeker studied congenital deaf-mutism in a northern Belgian province. Of a total of 110 persons ascertained, 61 had a nonhereditary cause and 5 had a hereditary mechanism other than an autosomal recessive one. The remaining 44 cases were assumed to be on the basis of autosomal recessive inheritance. A frequency of 0.0225 per cent for these cases agreed well with that found in other studies; 10 per cent of the parents were consanguineous; first cousin marriages accounted for 6 per cent. So high a consanguinity rate suggests a very low gene frequency (about 0.004) and a much lower phenotype frequency than that observed. The author suggested that the discrepancy could be accounted for by assuming that two or more genes are responsible for deaf-mutism. In some parts of the province studied, the frequency of persons heterozygous for at least one of these genes was calculated to be as high as 0.311.

837. Larsson found otosclerosis in 12 to 15 per cent of both the sibling group and the parent group when the families of 262 propositi with otosclerosis were investigated. He concluded that the findings prove to be most consistent with unifactorial autosomal dominant inheritance with 25 to 40 per cent penetrance.

XIV. ENDOCRINE SYSTEM

838. The pituitary. Martin reported on two unrelated families with congenital pitressin-sensitive diabetes insipidus. Here, as in the literature, the inheritance seemed to be that of a simple dominant gene, but a puzzling feature is a deficiency of affected females. Below are his data on familial diabetes insipidus with dominant inheritance. Hypertonic saline and nicotine failed to stimulate production of antidiuretic hormone. The defect may concern primarily the osmoreceptor mechanism rather than the site of production of antidiuretic hormone.

MALE		FEMALE	
AFFECTED	NONAFFECTED	AFFECTED	NONAFFECTED
79	81	64	87

Carsner and Rennels studied the primary site of gene action in anterior pituitary dwarf mice.

The thyroid: 839. An issue (Vol. 16, No. 2) of the *British Medical Bulletin* was devoted to the thyroid gland. Dictated by the important developments of recent years, particular emphasis was given to the genetic aspects. At least three of the fifteen papers concerned genetics directly, and the remaining twelve had important through indirect bearing on genetics. Trotter discussed deafness and thyroid dysfunction, dealing particularly with Pendred's syndrome, a defect in thyroxine synthesis inherited as an autosomal recessive trait. Although previously considered a rarity, it is now clear that it may be responsible for as much as 5 per cent of congenital nerve deafness. McGirr discussed genetic goitrous cretinism. Kitchin and Evans reviewed genetic factors in thyroid disease with particular reference to the increased risk of nontoxic goiter in persons who cannot taste PTC. Clements discussed naturally occurring goitrogens as studied in Australia. There may be, it would seem, genetic differences in vulnerability to the effects of these agents.

Blizzard discussed inherited defects of thyroid hormone synthesis and metabolism. Four specific defects of synthesis have been identified: (1) inability to trap iodide, (2) inability to oxidize iodide to elemental iodine, (3) inability to conjugate iodinated tyrosines to form calorigenically active iodinated thyronines, and (4) inability to dehalogenate "free" iodinated tyrosines. The existence of several other inherited defects of thyroid hormone synthesis is probable: (1) inability to halogenate tyrosines in the presence of elemental iodine, (2) inability to hydrolyze thyroglobulin, and (3) abnormal formation or release of thyroglobulin or "thyroglobulin-like" substance. Probably hereditary defects in thyroid hormone transport in the blood, including excessive (¶534) and decreased (Tanaka and Starr, 1959) thyroxin-binding protein have been identified. Finally, it is possible that genetic defect(s) in metabolism of thyroxine at the target cells exists. The methods for determining the nature of the defect were discussed.

Fraser, Morgans, and Trotter studied the syndrome of sporadic goiter and congenital deafness (Pendred's syndrome) in eighteen families. The inheritance

appeared to be autosomal recessive. The main feature was an inability to form organic iodine compounds at a normal rate. In all affected persons, potassium perchlorate administered one hour after an oral dose of radioiodine resulted in partial discharge of the radioiodine in the thyroid. The thyroid was enlarged in all affected persons; only a few were hypothyroid. The deafness is not a result of hypothyroidism but rather is an independent expression of the same gene defect. Fishman and colleagues described the same condition in 4 of 7 siblings. Bilateral nerve deafness was present apparently from birth. All were euthyroid and normally intelligent. Fishman and colleagues and also Smith reported on studies of Pendred's syndrome.

Choufer, Kassenaar, and Querido discussed that variety of congenital hypothyroidism in which the defect concerns the normal dehalogenation of iodotyrosines.

Rupp, Chavarria-Bonique, and Paschkis described 2 sisters who had goitrous cretinism and were members of a family with a high frequency of goiter. Protein bound iodine was normal and there was high thyroid accumulation of I^{131}, but I^{131} was not discharged by thiocyanate. The circulating protein bound iodine was not in the form of either thyroxine or triiodothyronine. The authors suggested that a previously unknown failure in the synthesis of thyroid hormone may be involved.

Werner, Block, and Mandl studied a family in which a brother and sister and a first cousin had unusual quantities of circulating iodoproteins, presumably peptide-linked iodoamino acids. Goiter was present in 2; hypothyroidism was present in all 3. Iodoproteins are defined as those which contain iodinated amino acids in polypeptide linkage, in contradistinction to carrier proteins upon which the iodinated compounds are adsorbed. The iodocompounds of the latter group are readily released upon butanol extraction, whereas those of the former group remain in the insoluble fraction.

Stanbury and Chapman described a 15-year-old boy, hypothyroid from birth, who developed a goiter shortly before the period of investigation. An only sibling was normal, but the parents and both pairs of grandparents were related. The father had a goiter and at least 7 female relatives through both the parents had goiters. The mother and maternal grandmother had had numerous local mastectomies for cystic disease. Although the thyroid gland was intensely hyperplastic on biopsy examination, studies revealed very little uptake of I^{131} by the thyroid, and very little I^{131} in the gastric juice and saliva could be demonstrated. The authors concluded that a genetic defect in the iodide concentrating mechanism ("iodide trap," "iodide pump") exists in the thyroid, gastric, and salivary glands of this patient. On the suspicion that the consequences of the iodide-concentrating defect could be overcome by high concentrations of iodide in the blood, such was given by mouth. In 4 weeks, the basal metabolic rate steadily rose from minus 38 to minus 1, signs and symptoms of hypothyroidism disappeared, and the goiter diminished to about one-third its pretreatment size.

Zondek and Leszynsky described 3 siblings with goitrous cretinism caused by inability to hold inorganic iodide and convert it to organic iodine. The feature of interest was that in each of the 3, short-term administration of massive doses

of active thyroid (90 mg. of Triac or its equivalent as desiccated thyroid for 6 to 9 days) resulted in protracted clinical remission without additional therapy for as long as 8 months. Tests of thyroid function at 2, 3, and 4 months "revealed a practically normal pattern."

In 5 persons from two sibships, McGirr and colleagues described a new inborn error of thyroid metabolism leading to goiter and cretinism. The disturbance apparently concerns the formation of an abnormal iodinated compound which liberates thyroxine with difficulty.

840. Shepard and Gartler found an excess of PTC nontasters among patients with congenital athyreotic cretinism and among their parents. They postulated that dietary consumption of goitrogenic thiocarbamide substances may be involved in the pathogenesis of some cases of athyreotic cretinism. "If the preceding hypothesis is correct, one would expect a lower incidence of athyreotic cretinism among populations (for example, Chinese and Negro) where the incidence of nontasting is low or in countries where the diet contains minimal amounts of thiocarbamides."

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841. Goldberg, in studying 123 cases of hypothyroidism, found fifteen families with multiple affected members, but in thirteen of these the husband and wife were affected. He raised the possibility that intrafamilial virus infection with thyroiditis might be responsible for such a pattern of familial (or household) aggregation. He suggested that the Lawson kinemometer, a quantitative device for testing the Achilles' tendon jerks, might be a useful method for surveying families for hypothyroidism.

842. Hall, Owen, and Smart found circulating thyroid autoantibodies in 22 of 39 siblings of 11 patients with thyroid disease accompanied by circulating thyroid autoantibodies "in appreciable concentration." Eleven of the 22 showed no other evidence of thyroid disorder at the time of the examination. The authors advance these findings in support of the view that the predisposition to develop autoantibodies to thyroid is inherited as a dominant characteristic. Only 2 parents of probands were examined.

Blizzard and colleagues found antithyroid antibodies in the serum of 11 of 67 mothers of patients with cretinism, a frequency much greater than in the general population or in pregnant women. Only 2 of the 11 mothers had known thyroid disease. The other 9 probably had not yet been affected because of greater resistance of adult than fetal thyroid tissue to destruction. A cytotoxic factor for thyroid tissue grown in tissue culture was identified in the serum of 2 mothers.

Working independently but along similar lines, Sutherland and four colleagues described "familial nongoitrous cretinism apparently due to maternal antithyroid antibody." The mother, a Negro, had had thyroiditis in childhood, was hypothyroid, and gave birth to 2 infants who were hypothyroid at birth and to a third who possibly was. The first infant died with a fibrotic thyroid gland. The third infant lived, with evidences of partial retention of thyroid function. Substitution therapy during the third pregnancy may have been responsible

Fig. 52.—Pseudospeudohypoparathyroidism.

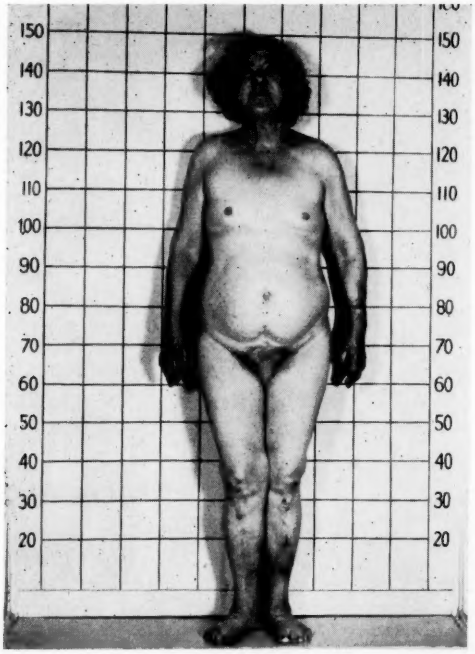


Fig. 52*A*.—A. M. (857397), 62-year-old white female, suffers from pain and limitation of movement in the shoulders and to a lesser extent in the fingers. Both lenses have been removed for cataract. The patient is severely but not unpleasantly demented. Chronic alcoholism may contribute to the dementia. The mother was short like the patient, with short fingers and toes. Two siblings were insane; whether these persons were short is not clear. However, 4 of 11 siblings had the same habitus as the patient, whereas the others were tall like the father. The comment of one observer was that the patient looked like "one of Rip van Winkle's nine pin dwarfs." Calcium, phosphorus, and alkaline phosphatase levels were normal. The spine shows marked hyperostotic arthritic change by x-ray.

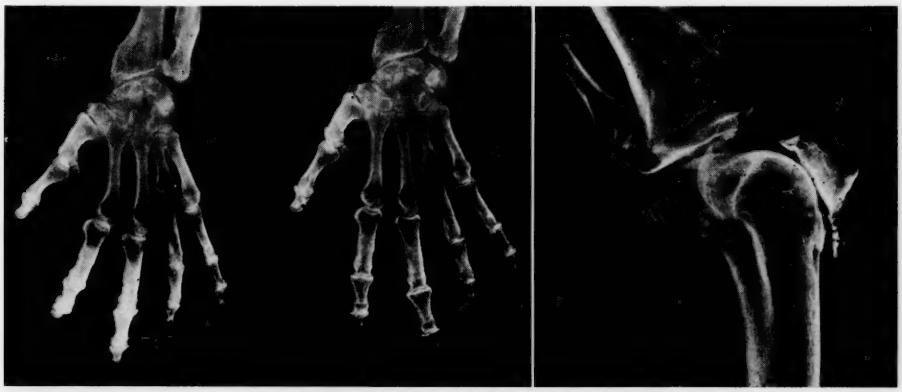
B. *C.*

Fig. 52*B* and 52*C*.—The characteristic brachydactyly is well shown.

in some way for the lesser damage to the thyroid of the third infant. Antithyroid antibody presumably of maternal origin persisted in the blood of the infant for 4 to 5 months, and there was no evidence of production of antithyroid antibody by the infant himself. Exchange transfusions at birth theoretically might reduce the total damage to the thyroid. These authors also could demonstrate that the mother's serum damaged fetal thyroid tissue in vitro.

843. Parathyroid. Jackson, Talbert, and Caylor described two families with multiple cases of parathyroid adenoma resulting in hyperparathyroidism. In one family 8 and possibly 9 persons were affected, in the other a father and son. The inheritance seems to be autosomal dominant. Greenbaum observed 4 cases of multiple parathyroid adenoma in one family. In one member, bronchial adenoma of the carcinoid type had occurred.

Cassidy and Anderson reported what they believe is the eleventh family with multiple cases of hyperparathyroidism produced by parathyroid adenoma and the sixth family in which at least one member had multiple parathyroid adenomas. They suggested that when hyperparathyroidism is familial, multiple parathyroid adenomas may be the rule and should be sought by appropriate surgical approaches.



D. *E.*

Fig. 52*D* and 52*E*.—Roentgenologic views. *D*, Brachydactyly. *E*, A very long spur extends from the upper margin of the patella. Bony exostoses frequently occur in these cases and may appear not unlike those of diaphyseal aclasis (multiple hereditary exostoses). Probably they are fundamentally of the same nature as the ectopic ossification that occurs at many sites.

Chaptal and colleagues reported studies of familial hypoparathyroidism. Peden described a large kindred in which hypoparathyroidism was transmitted as a sex-linked recessive trait. In the family studied by Cochrane, Morse, and Landrigan, hypoparathyroidism was associated with pernicious anemia and adrenal insufficiency.

About 20 years ago, Albright, Burnet, and Smith described 3 patients with clinical and chemical features of hypoparathyroidism but no response to the ad-

ministration of parathormone. They termed the condition pseudohypoparathyroidism. Somatic features characteristic of the condition were short, "thick-set" habitus, round face, short metacarpals, dull sensorium, and subcutaneous calcification. Gentili and Bottone studied a 5-year-old patient with pseudohypoparathyroidism and concluded that the fundamental defect is in the renal tubule.

Fig. 53.—Short fourth metacarpal in the Turner syndrome. Shown for comparison with Fig. 52.

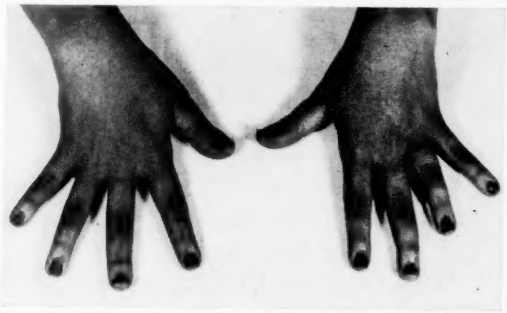
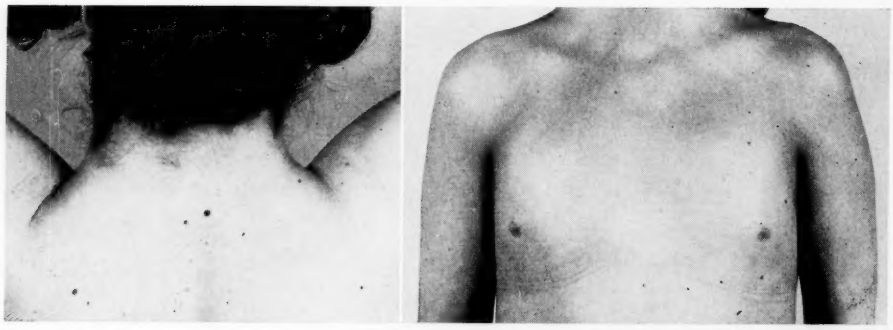


Fig. 53*A*.—Short fourth metacarpal.



B. *C*.

Fig. 53*B* and 53*C*.—Also shown are the low hairline, numerous pigmented nevi, web neck, and broad, shieldlike chest with wide intermammary distance (compare Fig. 5*A*).

Later, Albright's group and others encountered patients with the same somatic features but without the chemical indications of hypoparathyroidism. This disorder, which was clearly familial, they termed pseudopseudohypoparathyroidism. Barr, Taylor, and Rabkin reported one case, and Tanz reported a mother and 2 children. Dickson and his colleagues discussed the neurologic, electroencephalographic, and genetic aspects. (See Fig. 52.)

Dickson and colleagues studied pseudohypoparathyroidism and pseudopseudohypoparathyroidism. Unfortunately, they persisted in using the tautologic adjective "heredofamilial." They found cases of the two conditions in the same family and suggested, as have others, that the latter state is a forme fruste of the former. Assuming this to be the case, the pedigree pattern is that of an autosomal dominant trait. Tanz observed 3 cases in one family.

Two unrelated patients with pseudopseudohypoparathyroidism were reported by Papadatos and Alivistatos. Van der Werff den Bosch reported pseudopseudohypoparathyroidism with gonadal aplasia. Specifically, in a group of 6 patients with pseudopseudohypoparathyroidism, 4 had gonadal aplasia and 3 of these were chromatin negative. Dwarfism and short metacarpals and metatarsals are features of gonadal aplasia (Fig. 53). However, caution should be exercised in suggesting that the two entities are fundamentally the same.

844. The pancreas. Heterogeneity within the larger group diabetes mellitus is always being sought. A disorder which possibly represents insulin insensitivity of insulin-dependent tissues is that of lipoatrophy and diabetes (Schwartz, Schafer, and Renold). Craig and Miller described the occurrence of this variety in 2 siblings.

In Hungary, Barta found a family history of diabetes in 15.4 per cent of 227 diabetic children and in 2 per cent of 900 healthy control children. The frequency in parents of diabetic children was 2.7 per cent and was zero in parents of controls.

Andersen and Lauritzen found that male diabetics with early onset of disease showed a significant excess of blood group O; females showed some excess. No difference in Rh groups was observed, but a significant excess of Le (a+) was found in both male and female diabetics. "Since Le (a+) persons are nonsecretors of A, B, and H substance . . . possibly nonsecretor status means an increased susceptibility to diabetes." These results are in conflict with those of McConnell and coauthors, who found an excess of A among diabetics.

Nicol and Smith reported on the structure of human insulin. Previously, six other species have been studied and the only difference found to be in three amino acids in the A chain at positions 8, 9, and 10, as indicated below:

MAMMAL	POSITION		
	8	9	10
Cattle	Alanine	Serine	Valine
Pig, sperm whale	Threonine	Serine	Ileucine
Sei whale	Alanine	Serine	Threonine
Sheep	Alanine	Glycine	Valine
Horse	Threonine	Glycine	Ileucine

To this now can be added:

Man	Threonine	Serine	Ileucine

The subject of spontaneous diabetes mellitus in animals was reviewed by Meier, by Keen, and by Wilkinson.

Green, Yerganian, and Meier described extreme elevation of α_2 globulins of the serum as a characteristic of spontaneous hereditary diabetes mellitus of the Chinese hamster (*Cricetulus griseus*). The characteristic preceded the onset of clinical diabetes and microscopic evidence of glomerulosclerosis. Less pronounced elevations of α_2 globulin occur in diabetes in man but usually only after the development of vascular complications. They speak of this finding as "a

possible genetic marker." Usually a genetic marker is used to indicate a trait determined by a gene at a different locus but possibly on the same chromosome pair, that is, genetic markers are used in linkage work. Elevated α_2 globulin is probably a pleotropic effect of the single genetic change responsible for diabetes mellitus. The misuse of "genetic marker" in this connection is comparable to the misuse of "linkage" to refer to syndromal association of multiple characteristics produced by a single gene.

845. Adrenal. Hill described a method for chromatographic separation of the urinary 17-ketogenic steroids lacking an oxygen at carbon 11 from those with an oxygen at that site. In normal children, the nonoxygenated: oxygenated steroid ratio was 0.24. In *congenital adrenal hyperplasia*, it was 2.3. The advantage of the test in pediatric practice is that it can be applied to isolated samples of urine.

Eberlein and Bongiovanni reviewed the pathophysiology of congenital adrenal hyperplasia, which, they point out, is "one of the most thoroughly investigated inborn errors of metabolism." Three clinically recognizable variants were noted: (1) the "compensated" and (2) the salt-losing forms, which have in common a defect in 21-hydroxylation, more marked in the latter, and (3) the hypertensive form, in which 11-β-hydroxylation is faulty and desoxycorticosterone is secreted in abnormal amounts. Common to all is progressive virilization beginning in utero and secondary to inadequate hydrocortisone synthesis. The last leads to excess ACTH secretion and the production of an as yet unidentified androgen.

Klevit also reviewed all aspects, including the genetic, of congenital virilizing adrenal hyperplasia.

Ainger and colleagues observed two kindreds in which two first cousins were affected by congenital adrenal hyperplasia. The type of disease was the same in the cousins of each set. They commented as follows: "Since the mutant gene is established to be present in one of every 125 persons, the occurrence of this condition in first cousins, particularly in the absence of consanguinity, would be extremely rare, approximately once in 3,000,000 births." This calculation is absurd, and it is not clear how it was derived.

Stempfel and Engel described a form of familial adrenocortical insufficiency which appeared to be a selective defect of hydrocortisone synthesis with normal aldosterone production.

Studying adult male, dichorionic, monozygotic triplets, Kappas and Gallagher reported on the patterns of adrenal steroid excretion before, during, and after ACTH administration. In 2, the pattern was virtually identical. The differences in the third were interpreted as a reflection of the differences in vascular supply during fetal development.

846. Obesity. Lane studied the infertility of genetically obese mice. All homozygous females are sterile, and fertility is sharply reduced in homozygous males. Transplantation of ovaries from obese to thin mice results in offspring. For this and other reasons, a pituitary basis for the infertility was suspected.

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By various methods, Lane showed that obese mice are capable of increasing pituitary gonadotropin production but that the production is less efficient than in nonobese mice. Fenton has evidence of strain differences in mice with regard to metabolic efficiency and the proneness to obesity on particular diets.

A single injection of aurothioglucose in appropriate dose produces persistent obesity in mice. Lesions of the hypothalamus are thought to be the basis of the hyperphagia and therefore of the obesity. Liebelt and colleagues found that there was a strain difference in this effect. CBA strains were more consistent in the effect than were others. In f_1 hybrids, the behavior corresponded to that of the CBA strain.

A good review of the genetics of obesity in animals and in man was provided by Mayer.

Steinberg commented on the genetics of obesity. Assuming that the genetic contribution to obesity is in most instances polygenic, he referred to the difficulties in analyzing continuous traits. He referred to the study of C. P. Davenport (1923) in which intrafamilial correlation for body build using the ratio weight: stature^2 seemed to indicate a significant genetic factor.

XV. EYE

847. From a study of orbital *hypotelorism* and related states, Currarino and Silverman provided useful data on the normal interorbital distance measured in skull roentgenograms in children from birth to the age of 12½ years.

Lees described congenital static *familial ophthalmoplegia*. There were ptosis, almost completely fixed eyes, nystagmoid jerks, and unequal pupils.

In 2 sisters with *congenital ptosis*, Jain found *synkinetic oculopalpebral phenomena*, e.g., convergence on raising the lids and abduction on looking down.

Hilgers discussed the heredity of *pterygium*, concluding that it occurs with equal frequency in men and women working indoors. He stated that in many families it behaved as a dominant trait. Schwartz reviewed the reports of familial pterygium and added the case of an infant in whom pterygium was noted at birth and whose paternal grandfather had the defect.

Maumanee described 8 cases of congenital *hereditary corneal dystrophy*. In one family, there were 6 known affected persons in three generations. A Negro brother and sister were also included. François and Evens described a new type of hereditary corneal dystrophy in mother and daughter and briefly reviewed other forms of hereditary dystrophy.

Gardiner and James suggested that there is an association between *congenital myopia* and maternal disease such as toxemia of pregnancy.

848. Burian, von Noorden, and Ponseti found anomalies in the angle of the anterior chamber in cases which can be construed as systemic connective tissue disorders: severe idiopathic scoliosis, idiopathic genu varum, Legg-Perthes disease, slipped upper femoral epiphyses, and Osgood-Schlatter's disease, in addition to the Marfan syndrome (¶825).

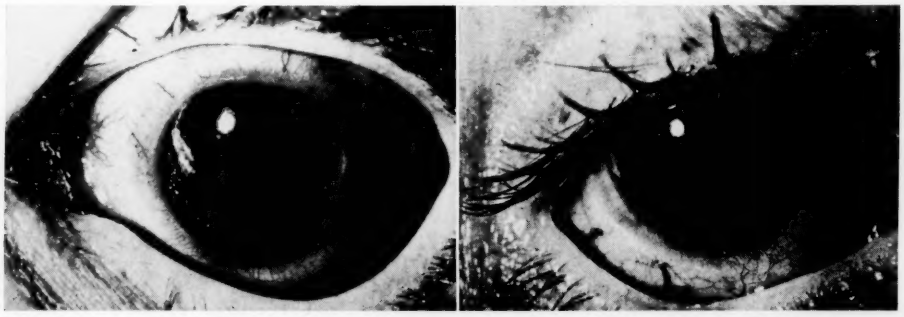
Shaw, Falls, and Neel ascertained 176 cases of *aniridia* (Fig. 54) in the lower Michigan peninsula. Of these, 118 were in patients living in Michigan on Jan. 1, 1959; 40 of them, isolated cases, were considered mutants. The frequency of aniridia in Michigan is about 1.8×10^{-5}, and the mutation rate is about 4×10^{-6} per locus per generation. (It might be better stated 4×10^{-6} per gamete per generation, because the possibility of production of the same phenotype by mutation at more than one locus has not been excluded.) The affected person may be visually handicapped because of nystagmus, cataract, or glaucoma. Fertility was slightly reduced in men. The most striking finding of the study was a 38:62 ratio of affected to normal children instead of the 50:50 ratio expected of a Mendelian dominant trait. (See ¶903 for a discussion of an anomalous segregation ratio in ectrodactyly.)

Heidensleben described the association of congenital koilonychia with *cataract*. The father of a patient had had spoon nails but no eye symptoms. Forni observed cataract in association with calcifying chondrodystrophy (see also Fig. 66).

849. Retina. Sorsby and Williams described two families each with multiple cases of *retinal aplasia*. In one family, the inheritance was clearly autosomal dominant, in the other probably recessive. Mental defect was associated in some. Kobayashi investigated the genetic aspects of retinitis pigmentosa.

Ricci discussed three types of vitreoretinal degeneration including as one type *retinoschisis*, which is inherited as a sex-linked recessive trait.

François, Barbier, and De Rouck observed *Fuchs' atrophia gyrata choroideae et retinae* in a 17-year-old girl who was the product of a first cousin marriage and who also had the *Alder anomaly* of the leukocytes (Fig. 55). Both parents had the Alder anomaly (azurophilic cytoplasmic granules in the neutrophils). They made the interesting suggestion that the grave eye condition is an expression of



A. *B.*

Fig. 54.—Aniridia in mother and son. The mother (M. I. B., 850678), age 39, has complete aniridia in the left eye (*A*), partial in the right (*B*). The son (G. B., 710796), age 6, has bilateral aniridia. Both have glaucoma; the combination of glaucoma and aniridia is sometimes called Axenfeld's syndrome. The photographs of the mother demonstrate the variability in expression of the gene for aniridia, even in opposite eyes of the same individual. The son also has inguinal hernia and acyanotic congenital heart disease, presumably ostium primum type of atrial septal defect. The relation to aniridia is uncertain. (Patients of Dr. A. E. Maumanee.)

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the homozygous state of the gene for the Alder anomaly. The leukocyte anomaly is known to behave as an autosomal dominant trait.

Macklin reported on a study of *retinoblastoma* in Ohio. Complete ascertainment of cases in persons born in a 17 year period was attempted. In 119 of 133 families, the disease occurred in only one person. Among fully known familial cases, 58.8 per cent included bilateral involvement, whereas the corresponding figure was 31.6 per cent for sporadic cases ($p < 0.01$). The longest interval observed between involvement of the two eyes was 51 months. Some of the patients with hereditary unilateral cases may not have lived long enough to develop involvement of the other eye. However, that unilaterality can occur in the genetic form is undoubted since one such patient has lived 43 years with involvement on one side; a brother and a child have bilateral disease. Only two instances of parental consanguinity, occurring in one family, were observed,

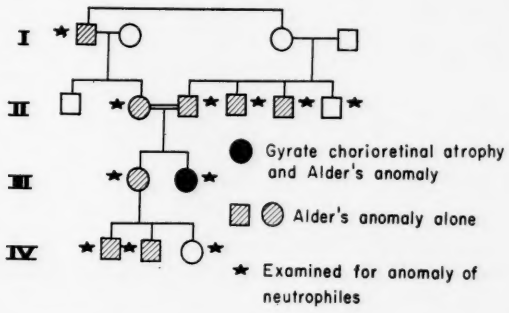

Fig. 55.—Alder anomaly and chorioretinal atrophy. On the basis of the pedigree shown here, Francois and his colleagues postulate that gyrate chorioretinal atrophy is the expression of the homozygous state of the gene which in the heterozygote causes only Alder's anomaly of the leukocyte. (From Francois, J., Barbier, F., and De Rouck, A.: Acta genet. med. et gamell. 9:74, 1960.)

rendering recessive inheritance unlikely. However, vigorous and widespread investigation of the 133 family trees—for which Macklin is noted and to be commended—showed peculiarities indicating a much lower rate of penetrance than previously thought if retinoblastoma is indeed the result of a gene capable of expression in the heterozygote. For example, she observed 2 affected siblings from normal parents and in another family 3 affected siblings from normal parents. In one large and much intermarried kindred, 8 cases were found, including 4 in affected offspring of a consanguineous mating of unaffected parents. There were other peculiarities, such as two instances of affected second cousins, one of a girl and her father's uncle, a boy and his first cousin twice removed, and so on. Taking these kindreds with multiple cases and counting up the minimum number of carriers, one arrives at an estimate of penetrance of the order of 20 per cent. Previous estimates have varied from 78 to 98.5 per cent. Estimated mutation rates are correspondingly lower: 1.76×10^{-5} to 0.63×10^{-5}. The mutation rate in Negroes appeared to be higher than in white persons, but there was a question

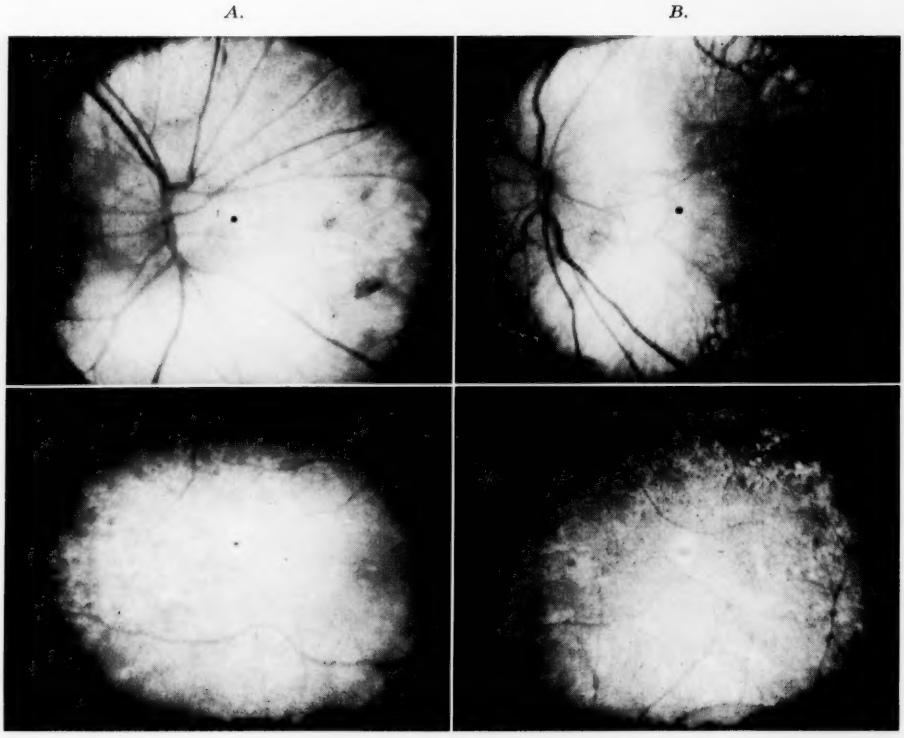

Fig. 56.—Choroideremia.—Shown are the right and left fundi. *A* and *B*, Affected son. *C* and *D*, Carrier mother. T. T., a 13-year-old white boy, had had progressive loss of vision for 3 years and night blindness for 8 years. He had 4 brothers and no sisters. The patient and 2 of his brothers have progressive, nerve type deafness, which in the proband began at age 4 years. The fundus in the patient is largely depigmented, and the straight choroidal vessels are visible. The changes in the right are more marked than in the left. The mother, presumably heterozygous for the choroideremia gene for which the son is hemizygous, is asymptomatic and shows pigmentary changes in the fundus. (Patients of Dr. A. E. Maumanee.)

as to whether physicians might be more reluctant to report private white patients to a research study. Possibly, family investigations could not be as rigorous in the case of Negro families; information on collateral relatives might be more limited. In this study, about one in each fifteen normal parental pairs who had had one child with retinoblastoma had another affected child.

Grice and Hutchison described retinoblastoma in a dog.

Reichel presented a family with 4 cases of *congenital, lethal pseudoglioma* occurring in 4 males in two generations and apparently displaying sex-linked recessive inheritance. (Pseudoglioma is the term applied to an inflammatory exudate in the vitreous simulating glioma or retinoblastoma.)

850. Harrison, Hoefnagel, and Hayward described *congenital total color blindness* in 2 brothers one of whom also had Charcot-Marie-Tooth disease. There were no other color blindness in the family and no known parental con-

sanguinity. This rare disorder has a frequency of about one in 300,000 and is transmitted as an autosomal recessive trait. In one brother, these workers had an opportunity to examine the eye. They demonstrated marked paucity of cones in the foveal area and concluded that the cones present were abnormal.

Pameyer, Waardenburg, and Henkes described 3 male patients with *choroideremia* (Fig. 56) and 6 female carriers in two families. This disorder is of considerable genetic interest, being inherited as a sex-linked intermediate trait. Males have a striking fundus picture and serious visual impairment. Female carriers have changes observable by fundoscopy but no functional defect. The authors suggest that choroideremia may represent an "abiotrophic process of the 'tapetum nigrum' with a secondary progressive dystrophy of the choriocapillary layer and outer retinal layers."

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XVI. GENITAL SYSTEM

851. Stern considered sex determination. General discussions of sex anomalies were given by Davidson and by Foss, among others.

852. The Klinefelter syndrome. In a survey of sex chromatin pattern in mentally retarded children (IQ 55 to 85), de la Chapelle and Hortling found 3 cases of the chromatin-positive Klinefelter syndrome in 342 boys and one case of the chromatin-negative Turner syndrome in 269 girls.

By the leukocyte method, Halbrecht found chromatin-positive nuclear sex in 6 out of 30 azoospermic males and in one out of 8 newborn "males" with hypospadias, a confirmation of numerous previous reports. The author concluded wisely that nuclear sex determination should be included in the investigation of cases of male infertility.

Stewart and colleagues made a systematic comparison of clinical and hormonal features in 16 cases each of chromatin-positive Klinefelter syndrome, chromatin-negative Klinefelter syndrome, and fertile men. In both forms of the Klinefelter syndrome, the testes and prostate were small and there was a high level of follicle-stimulating hormone. The chromatin-positive persons showed striking disproportion in body measurements. This was apparent in their long-leggedness, a feature which was not present in the other two groups.

The proceedings of a symposium entitled "Sex Differentiation and Development" and held in 1958 at the Royal Society of Medicine (London) under the sponsorship of the Society of Endocrinology were edited by Austin. The usual delays of publication combined with the printing strike result in some portions being of historic interest only. A useful, well-illustrated discussion of the testicular histologic state in the Klinefelter syndrome is provided.

Mosier, Scott, and Dingman (also Mosier, Scott, and Cotter) emphasized the high frequency of persons with sexually deviant behavior in Klinefelter's syndrome. Of 600 institutionalized male psychopaths, one per cent had cases of the chromatin-positive Klinefelter syndrome.

853. Gonadal aplasia. Jones reported on 7 cases of symmetric peripheral edema always in the feet, sometimes in the hands as well, in infants. Five of the 7 were girls, and of these, 3 had the chromatin-negative Turner syndrome. The remaining 4 cases were interpreted as the Bonnevie-Ullrich syndrome. In none was there a family history of anything interpretable as the same disorder. Richart and Benirschke described the diagnosis of the Turner syndrome in the newborn.

On the basis of 19 cases, Kosowicz described deformity of the medial tibial condyle as a characteristic feature.

Izakovič described "sisters" with typical chromatin-negative Turner syndrome. Paradoxically, despite the chromatin-negative buccal smear, the leukocytes showed the drumsticks indicative of the chromatin-positive state. The paradox has been noted by others in cases of the Turner syndrome. Whether chromosomal mosaicism (¶714 ff.) is the basis should be investigated.

Chokas described the instructive case of a 21-year-old married woman with hypertension who was proved to have the chromatin-negative variety of gonadal aplasia. He emphasized that this disorder should be considered in cases of unexplained hypertension in young "females." The patient had a horseshoe kidney. Of note was the occurrence, in the same patient, of rheumatoid spondylitis, a disease which seems to have a rather strong genetic determination and which occurs predominantly in males. He uses the unfortunate expression "rheumatoid-spondylitis, a genetically-linked disease" (see ¶350).

Davidson and Heath reported the clinical and autopsy findings in a case of gonadal aplasia with pulmonary hypertension. The patient was 37 years old at time of death. The authors concluded the cor pulmonale to have been related to the patient's kyphoscoliosis. However, the possibility of primary pulmonary hypertension seems strong, since systemic hypertension without demonstrable cause occurs in the Turner syndrome and since the description of the spinal deformity does not suggest that it was severe.

Fraccaro, Gemzell, and Lindsten studied the plasma level of growth hormone in 4 cases of the Turner syndrome. Three were XO; one was an XO/XX mosiac. All 4 showed an elevated plasma level of growth hormone.

Bahner and colleagues reported a chromatin-negative XO female who at the age of 31 gave birth to a normal son. Menses and breast development were normal. Short stature (136 cm.) was the only somatic peculiarity. Studies revealed 45 chromosomes with an XO sex chromosome complement in the mother and an apparently normal chromosome constitution in the son.

Engstrom and Stoddard described 2 patients with negative chromatin pattern but ovarian gonadal tissue. Neither was short or had any somatic anomalies. The chromosomes were not studied.

Klotz describe 7 persons with a syndrome comprising nonfunctioning ovaries, genital infantilism, and negative chromatin pattern. Five were short, some were mentally defective, and horseshoe kidney, harelip, Mongoloid facies (2), diencephalic epilepsy, pseudohypothyroidism, and epilepsy (2) occurred. The cases differed from the usual Turner syndrome in the fact that pituitary gonadotropins were not elevated.

854. Syndrome of testicular feminization. Puck, Robinson, and Tjio confirmed the findings of Jacobs and coauthors (¶552) that the chromosome count is 46 and the sex chromosome constitution XY in the syndrome of testicular feminization (male pseudohermaphrodism). They point out that the pedigree data are consistent with either sex-linked recessive or autosomal dominant inheritance. They favored the latter possibility since there seemed to be no close linkage with hemophilia or with color blindness. The latter impression was based on two reports: Jacobs and coauthors and Stewart separately described (¶552) a family in which one sibling had the syndrome and color blindness, one had only the syndrome, and a third normal male had only color blindness. Puck, Robinson, and Tjio furthermore interpreted the case of Nilsson (¶385) as probably one of this syndrome in combination with hemophilia. A brother of Nilsson's patient had only hemophilia. They pointed out the preponderance of "females" on the mother's side in Nilsson's pedigree.

Chu, Grumbach, and Morishima also found an XY sex chromosome contitution. They discussed the genetics and concluded that the evidence at hand does not permit a decision between sex-linked recessive or sex-limited autosomal dominant inheritance.

855. Others. In a 3 year period, Cunningham observed and treated acute *testicular torsion* in 3 brothers ages 14, 15, and 21. The father and 2 other brothers had hypermobility of the testicle but had not suffered acute torsion. The anatomic peculiarity predisposing to torsion was presumably inherited.

Lynch and colleagues described a family in which *male hypogonadism* was associated with congenital ichthyosis. Follicle-stimulating hormone titers were low (in contradistinction to the Klinefelter syndrome), leading to a designation of secondary hypogonadism by the authors. Testicular biopsy showed complete absence of Leydig cells and considerable scarring and atrophy of germinal tubules. Pectus excavatum, kyphosis and scoliosis, and a cleft between the first and second toes also occurred in members, but the distribution in the family does not suggest a relationship to the hypogonadism and ichthyosis. The genetic possibilities considered by the authors were the following:

1. That the inheritance is sex-linked recessive: (a) that a mutant at a single locus is responsible for both hypogonadism and ichthyosis and (b) that genes responsible for the two characters are closely linked. Sex-linked recessive inheritance of isolated congenital ichthyosis has been reported. No recombinant individuals were observed, but unfortunately in no sibship containing doubly affected males were any other males examined.

2. That the inheritance of one or both traits is autosomal dominant with sex limitation. Perhaps this would be a plausible explanation for the hypogonadism. However, assuming that FSH is the same in males and females and that a defect in its formation is indeed the basis of this syndrome, the females might be expected to express the gene—which would never pass beyond the new mutant. Furthermore, complete male sex limitation of ichthyosis does not seem plausible. That male hypogonadism is a sex-limited autosomal dominant trait and ichthyosis a sex-linked recessive one could explain the entire pedigree.

In the syndrome of Rüd (MacGillivray, 1954), ichthyosis and secondary hypogonadism occur together, but in addition severe mental deficiency and epilepsy are features.

XVII. MUSCLE

856. Progressive muscular dystrophy. Levin, Baens, and Weinberg reported on a large Negro sibship with multiple cases of Duchenne progressive muscular dystrophy, emphasis being placed on the cardiac involvement. One patient showed at autopsy extensive endocardial fibroelastosis, suggesting that the latter lesion may even in the "primary" disease be secondary to a myocardial defect. We have observed at autopsy endocardial fibroelastosis in one of male identical twins, both with progressive muscular dystrophy. One twin died suddenly at the age of 13 years; the other is still living. (Endocardial fibroelastosis has also been described in the Hurler syndrome and in glycogen disease of the heart.)

Dubowitz presented evidence for the autosomal recessive transmission of the Duchenne type of progressive muscular dystrophy. He described the disease in 2 sisters, offspring of a first cousin mating.

Jackson and O'Donnell described atrial flutter in a 39-year-old white man with progressive muscular dystrophy. Weakness of the extremities began at about age 20, and foot drop had been present for about 10 years. Whether this was a case of the sex-linked recessive Duchenne muscular dystrophy with unusually late onset or a different variety cannot be determined. We have the impression that cardiac involvement occurs only in the Duchenne type (and, of course, in myotonic dystrophy).

Berneske and colleagues treated 33 patients with muscular dystrophy with 2,000 I.U. of alphatocopherol succinate daily or a placebo. Those who received vitamin E had the same course as those receiving placebo.

Kruh and colleagues compared the metabolism of myosin and water-extractable proteins in normal mice and in mice with the hereditary muscular dystrophy discovered at Bar Harbor. They did not prepare pure aldolase since this would have required too many animals, but they have previously demonstrated that the total water-extractable proteins have the same gross behavior as aldolase. Their findings using glycine-2-C^{14} indicate an accelerated turnover of muscle proteins in the dystrophic mice. In normal mice, the life span for the myofibrils was estimated at 20 days.

McCaman found in dystrophic mouse muscle an excess of enzymes requiring TPN as a cofactor, especially glucose-6-phosphate dehydrogenase, and a deficit of enzymes requiring DPN as a cofactor. West and Murphy did histopathologic studies. Ross, Pappas, and Harman reported electron microscopy studies of hereditary muscular dystrophy in mice.

Chung, Morton, and Peters found that heterozygous carriers of muscular dystrophy in chickens had higher mean values of serum aldolase and transaminase and wider breasts than do the homozygous normals. Serum enzymes were of doubtful help in identifying heterozygous carriers of muscular dystrophy in man.

857. Myotonic dystrophy. The diagnosis was discussed by Ziegler, Geha, and Rose. Gordin and colleagues reported 5 cases of myotonic dystrophy. Vanier described myotonic dystrophy in a group of children, the youngest of whom was only 9 months old. The mother of the infant "has myotonic grip, of which she is aware but which is not a cause of severe disability. Her temporal muscles are wasted. Her brother is severely affected and has cataracts. The maternal grandfather's sister had cataracts." (See Fig. 57.)

Ramelli found that all of 6 male patients with myotonic dystrophy were chromatin negative. In his title, he speaks of "chromosome sex." Since buccal smears and not chromosome preparations were studied, the title is inappropriate. This improper type of designation is used by some other writers as well.

Fig. 57.—Myotonic dystrophy in a 7-year-old child. In A. P. T. (A69395), clubfeet were present at birth. There was always difficulty walking, and the question of whether she was "spastic" was raised repeatedly by physicians. At the age of 7 years, the findings included slight mental retardation, little facial movement, especially of the muscles about the mouth, which were feeble, difficulty raising the head from the couch, small tongue, marked lordosis, and myotonic reaction of percussed muscles. The mother had had a noticeable myotonic grip since the age of 16 years, it having been first noted when she shook hands with her escort after an evening of dancing and the hands could not be disengaged for some time. Two paternal aunts were similarly affected.

Katzenstein-Sutro and Bosch-Gwalter described in members of three generations *congenital myotonia of Thomsen*, with muscle hypertrophy, transmitted as an autosomal dominant trait. With advancing years amelioration tended to occur, and in one patient there was complete remission at the age of 60 years. There was no ribosuria. Vitamin E was not beneficial.

858. Central core disease was described by Shy and Magee in 1956. It is a nonprogressive, apparently congenital disorder manifested by muscle weakness which is most severe in the proximal limb musculature, especially in the legs. The pedigree shown by these authors suggested autosomal dominant inheritance.

Dubowitz and Pearse described a peculiar distribution of enzymes (histochemically displayed) in cases of central core disease. Whereas in the normal state two populations of muscle fibers may exist (one with enzyme and one without), in central core disease all muscle fibers are stained.

859. Klein discussed hyperkalemic *familial periodic paralysis*, which is inherited as a dominant characteristic. Attacks tend to occur during rest after exercise and are precipitated by cold, pregnancy, and fasting. Case reports of familial periodic paralysis were provided by Armen.

860. Cases of *paroxysmal recurrent rhabdomyolysis* were reported by Haase and Engel, by Denson, and by others. Wheby and Miller described it in 2 sisters. Denson used the ammonium sulfate test and paper electrophoresis in the diagnosis.

861. Alter and Talbert described monozygotic twins only one of whom had *myasthenia gravis*. In the unaffected twin, even a curare provocative test was negative. Foldes and McNall reported myasthenia gravis in a 73-year-old woman and in 2 daughters, ages 45 and 38 years.

Moebius syndrome, congenital paralysis of the sixth and seventh nerves, is also called congenital facial diplegia. Multiple cases in families have been described, e.g., by Wilbrand and Saenger in 1921.

In 2 patients, Wallis found marked creatinuria and suggested that the disease is a myopathy rather than a nuclear agenesis.

XVIII. NEOPLASMS

862. A symposium. Genetics and Cancer. A Collection of Papers Presented at the Thirteenth Annual Symposium on Fundamental Cancer Research, 1959, published for the University of Texas M. D. Anderson Hospital and Tumor Institute, Austin, 1959, University of Texas.

Here are a few of the many interesting contributions: Darlington (Oxford) reviewed his theory that a plasma gene, probably RNA-protein in Nature, is primarily involved in carcinogenesis. Schultz (Philadelphia) reviewed the subject of somatic mutation with particular reference to neoplasia. Levan (Lund) spoke on the relation of chromosome numbers to the origin and progression of tumors. Shope (New York) discussed the tumor-inducing properties of the fibroma-myxoma virus complex. Hauschka and colleagues (Buffalo) discussed the sex-linked incompatibility of normal and primary neoplastic tissues transplanted from male to isologous female mice. Anderson (Houston) has studied the genetics of bovine ocular carcinoma. Bonner (then Yale) reviewed work by him and his colleagues on tryptophan synthetase (see ¶674).

Schull (Ann Arbor) and Morton (Madison) discussed methods in human genetics with, of course, particular reference to human cancer. The following quote from Schull is noteworthy:

As one scans the literature on genetic factors in the more common cancers, one cannot help but be impressed by the frequently acrimonious and, to me, generally puerile polemic on "controls." This is the favored device of the statistician for obfuscating an issue. One is impressed by the surprising uniformity of findings despite the plethora of different controls in the various studies. This leads one to speculate on the value of the present approach. Thus, in a recent study (Woolf, 1955) of the genetic aspects of carcinoma of the breast and stomach, for example, the objectives of the study were said to be "(1) to determine whether familial tendencies could be shown for the two types of neoplasia, (2) to determine the magnitude of these tendencies, if present, and (3) to determine whether the familial tendencies, if present, are limited to specific organs or are of a more general nature that predispose to cancer irrespective of location." A good many man-hours later, the author is able to conclude that (1) relatives of the stomach cancer propositi exhibit a significantly higher frequency of stomach cancer deaths than expected in the general population (two- to threefold increase); (2) female relatives of breast cancer propositae exhibited a significantly higher proportion of deaths from breast cancer than expected in the general population (two- to threefold increase); and (3) in both breast and stomach carcinoma the inherited tendency was organ-specific. Similar findings have been reported for cancer of the breast by Jacobsen (1947), Penrose, Mackenzie, and Karn (1948), Macklin (1960), Oliver (1960), and Anderson (1954). All of these workers find approximately a two- to threefold increase in breast cancer among the female relatives of breast cancer index cases. Studies of cancer of the corpus of the uterus (Brøbeck, 1949), and of the cervix and corpus combined (Murphy, 1952) result in findings comparable to those for cancer of the breast. And finally, Videbaek's study (1947) of leukemia in Denmark follows the same general pattern found in cancer of the breast, uterus, and stomach.

Now what do these results tell us about the role of genes in the etiology of cancer? To be argumentative, I will take the position that they tell us virtually nothing. It seems to me that we might have anticipated the general level of effect which is detected. Certainly clinical impressions alone, subjective though they may be, would lead one to expect a relatively small increase in risk to the relatives of index cases. That there would be an increase and that it would be small follows from the correlation among relatives not only of genotypes but of environments as well, and a large increase could hardly escape clinical recognition. We are, it seems to me, destined to find a small effect, and this is what we find. That this effect cannot be interpreted in meaningful genetic terms may stem from the heterogeneous nature of the end point which we measure. Personally, I fail to see how the present approach can ever materially advance our understanding of the origins of the more common cancers.

A more profitable approach would seem to be a concentration on known high risk families, and a concerted effort to exploit the untapped information in the rare cancers. I certainly do not envisage a study oriented along the usual lines, retrospective and with emphasis on simple pathologic classification. Rather, an effort toward eliciting biochemical or physiologic differences among individuals within the aforementioned families might provide the "handle" whereby one gains entry into the problem. Finally, let me clearly state that I do not mean to imply that studies such as the ones we have just mentioned are totally without value. These studies have provided important demographic information, and they have served to reinforce certain impressions and areas of our knowledge. I am, however, opposed to the needless replication of these studies which has occurred in the past. I can see no useful purpose served by an effort to add "decimal points" to the risk of occurrence among relatives of probands with breast, stomach, etc., cancer.

863. Green, Inkelas, and Allen presented an interesting theory that *Hodgkin's disease* is a maternal to fetal lymphocyte chimera and some skin-grafting experience in support of the theory. Maternal lymphocytes probably can enter the fetal circulation. Artificially produced lymphocyte chimeras in mice manifest weight loss, diarrhea, dermatitis, and a peculiar atrophy and granuloma formation in the spleen and lymphoid organs. Occasionally, lymphomas also develop. These workers compared the survival times of maternal skin and unrelated skin grafted to recipients with Hodgkin's disease. Maternal skin survived longer.

Although the authors are aware of the several possible explanations for the observations and of the other related experiments which must be done, they suggest that the findings support the theory that Hodgkin's disease is the result of maternal to fetal lymphocyte chimerism.

864. Yates and Pearce, in analyzing 473 cases of *astrocytoma*, found that although ABO blood groups were "normally" distributed in this disease before 1946, after 1945 there was a very significant ($p = 0.0002$) reduction in group O.

865. In a monograph on genetic aspects of *cerebral glioma* and its relation to status dysraphicus, van der Wiel gave an amazingly long list of primary and accessory stigmata which he suggests may be indicative of genetic disposition to glioma. Primary stigmata include spina bifida, kyphoscoliosis and other disturbances of the vertebral column, funnel chest, hollow feet or unduly high arches, club foot, Horner's syndrome with heterochromia iridis, etc. Accessory stigmata include clinodactyly, camptodactyly, webbed digits, winged scapula, inequality in the size of the breasts, high palate, etc., etc., etc.

The families of 100 glioma probands and of 100 controls were studied. Unfortunately—especially considering the subjective nature of diagnosis of most of the stigmata under investigation—a single investigator did not examine all families personally, and the examinations of families were not blind.

The worker found that most of the stigmata were more frequent in glioma families and that within glioma families they were more frequent among first degree relatives than among cousins. He concludes that status dysraphicus is a background for glioma and that it is inherited as an autosomal dominant trait.

Kjellin, Müller, and Aström observed 2 or more instances of *brain tumor* in each of seven families (15 cases in all). In six of the seven families, the brain tumor was of the same histologic type and displayed the same biologic behavior, e.g., malignant glioma in a father and both of his children and in a mother and one of her 2 children; benign astrocytoma in both of twin boys, presumably monozygotic.

866. Beasley found, irrespective of specific intragastric site, a significant excess of blood group A in 746 cases of gastric cancer.

Macklin studied the families of 167 probands with *gastric cancer* and of 145 probands with *cancer of the colon*. There was a significant increase in the frequency of gastric cancer in the first group and of colonic cancer in the second group. Gastric cancer was not increased in the families of colonic cancer probands, neither was colonic cancer increased in the families of gastric cancer probands. No families of multiple polyposis were discovered in the colonic cancer group.

867. Woolf found death from *cancer of the prostate* to be three times more frequent in the male relatives of prostate cancer probands than in controls. The number of deaths from other types of cancer in male and female relatives was not significantly increased over that observed in controls. The results were considered compatible with an organ-specific genetic component in prostatic cancer.

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868. Zeligman described *Kaposi's sarcoma* in father and son. Although a characteristic ethnic occurrence (Italian and Jewish) has been noted, this is perhaps only the second instance of familial occurrence.

869. Gorlin, Fusaro, and Benton reported on *multiple glomus tumor* in 5 members of two generations of a family. The propositus was a 30-year-old physician. Autosomal dominant inheritance was proposed. Multiple glomus tumors tend to resemble cavernous hemangiomata. The distinctive feature is the presence of multiple layers of glomus cells lining the blood-filled cavities. The multiple tumors are present at birth or appear in the first two decades. The single glomus tumors usually develop later—at about age 33 years on the average—and are, unlike the multiple tumors, rather frequently subungual in location.

XIX. NERVOUS SYSTEM

870. General. Barrows vigorously attacked the use of eponyms in neurology, many of them for heritable disorders. One can only comment that occasional use will probably be inevitable because of the availability of no better label and the risk that a designation concocted on the basis of a presumbed pathogenesis may retard progress if the mechanism is in fact quite different.

Cumings discussed the chemistry of hereditary diseases of the central nervous system such as Niemann-Pick's disease, amaurotic familial idiocy, gargoylism, metachromatic leukodystrophy, the Krabbe or globoid body type of diffuse sclerosis, sudanophilic diffuse sclerosis, Merzbacher-Pelizaeus disease, and the Caravan type of diffuse sclerosis.

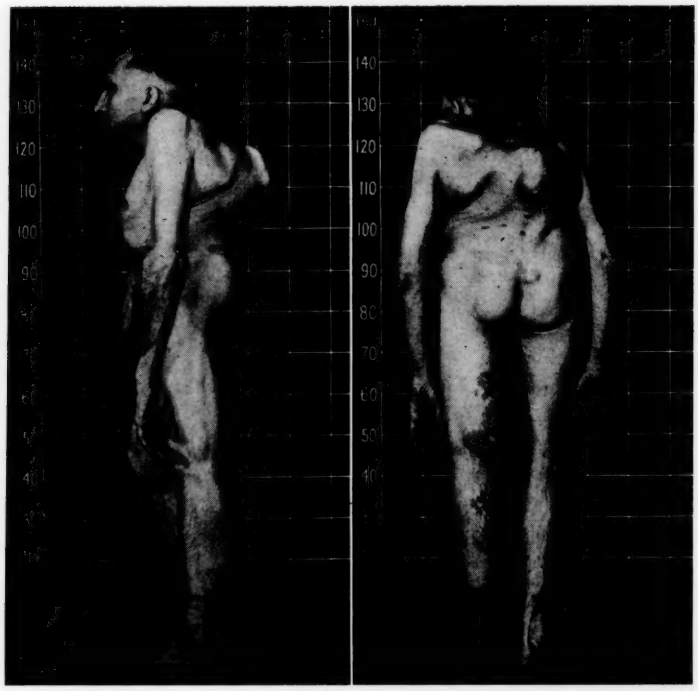
Phacomatoses: 871. Allibone, Illingworth, and Wright discussed 5 cases of *neurofibromatosis* of the vertebral column, a grave complication leading to marked scoliosis which is often the main manifestation of the disease (Fig. 58). In children, the skin manifestations may be minimal and overlooked, leading to a failure to recognize the cause of scoliosis. They quote Brooks and Lehman as suggesting that the complication begins as neurofibroma of periosteal nerves with reaction in the vertebrae, bone destruction, and bone regeneration.

872. Hasegawa and Ihrke described a sporadic case of *tuberous sclerosis* with unusually extensive sclerotic bone lesions of the spine and pelvis. Bilateral dislocation of the hips was present. Fibromata of the gingiva in tuberous sclerosis were described by Gorlin, Chaudhry, and Kelln. Iwamoto and Tomoda described a case.

873. See ¶939 for a discussion of certain aspects of von Hippel-Lindau's syndrome. (See Fig. 59.)

874. Oral changes in the *Sturge-Weber syndrome* were described by Gyarmati. There seems to be no good evidence that this disorder is heritable. Mul-

Fig. 58.—Neurofibromatosis with severe scoliosis and hypertension.



A. *B.*

Fig. 58*A* and 58*B*.—J. B. (513988), age 40 years, was one of 13 children from normal parents. Seemingly, only he had neurofibromatosis. At the age of 31 years, he was seen with neurologic manifestations interpreted as those of the Brown-Séquard syndrome. A neurofibroma of the spinal cord at the level of C6 was resected, and the patient had dramatic improvement. At that time, hypertension (155/115 mm. Hg) was present. When he was seen at the age of 40 years, blood pressure was 180/135 mm. Hg. However, the fundi showed only minimal changes. Five days after the examination and the photographs shown here, death resulting from cerebrovascular accident occurred. Autopsy revealed a large left-sided intracranial hemorrhage. There was no pheochromocytoma (see Fig. 14). There was marked buckling of the descending thoracic and abdominal aorta, probably producing severe narrowing of the right renal artery. A relation to the hypertension can only be postulated. Present are café-au-lait spots and other pigmentation and severe spinal deformity.

tiple familial cases have not, to our knowledge, been described. The etiology and pathogenesis remain obscure, just as in Ollier's enchondromatosis (¶912) and Albright's polyostotic fibrous dysplasia. The description of a chromosomal aberration (¶721) has not been confirmed in 3 cases studied in this laboratory.

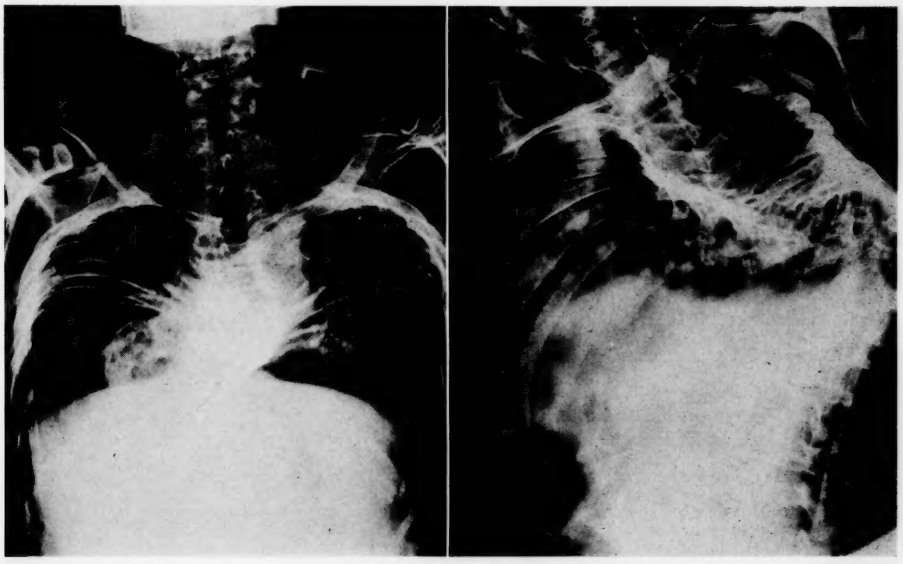
875. Sedgwick and Boder have collected 13 cases of the *ataxia-telangiectasia syndrome*. With those reported in the literature and described to them in personal communications, they have knowledge of a total of 52 cases. Reye and Mosman described a case in which symptoms of mucosal bleeding occurred as in the Osler-Rendu-Weber syndrome. Andrews, Kopack, and Bruton also described a case. Williams, Demis, and Higdon described a case and showed that the telangiectases are venous in nature.

876. Spinocerebellar degeneration. McNutt and colleagues concluded that *hereditary ataxia* is inherited as a dominant trait with expressivity varying from only pes cavus to marked neurologic disease. Their report does not state how many families were studied and does not grapple with the probability of heterogeneity in the condition. Carpilovsky described a large Brazilian kindred in which many cases of spinocerebellar ataxia occurred.

Hartman and Booth commented on the heart in 7 cases of *Friedreich's ataxia.* All of 6 patients on whom an electrocardiogram was available showed abnormalities. They point out that usually chronic interstitial myocarditis has been found at post mortem. (See Fig. 60.)

The association of the Klinefelter syndrome and familial cerebellar ataxia in the case of Hecht and Ruskin was probably coincidental.

877. Fullmer and colleagues found that 60 per cent of patients with *amyotrophic lateral sclerosis* show distinctive changes in the connective tissue of the skin. These were enumerated as (1) distinctive elastosis, (2) increased mucopolysaccharide (3) degeneration and elastosis of the arrector pili muscles, (4) focal areas of regenerated connective tissue, and (5) alterations of collagen. They do not as yet know whether the cutaneous changes antedate the appearance of neurologic disease. The cutaneous changes were observed in the disease in both Guam and the United States. It is disappointing that no clear statement is made about what, if any, clinically obvious changes in the skin were noted; presumably the skin appears normal. Elastosis seems a poor term.



C. *D.*

Fig. 58*C* and 58*D*.—The roentgenologic views indicate the severity of the spinal deformity. *C*, Postero-anterior view. *D*, Left anterior oblique view.

Green found amyotrophic lateral sclerosis in many members of four generations of a Pennsylvania Dutch family.

878. Asano and colleagues described a Japanese kindred with 4 and possibly 7 instances of a peculiar type of *progressive muscular atrophy.* Muscles in the distal portions of the extremities, especially the peroneal, became severely atrophied beginning in the first years of life, and sensibility of the feet was impaired. Further symptoms were dysarthria, choreic movements of facial and arm muscles, partial optic atrophy, scoliosis, incontinence, and mental deficiency. The deep tendon reflexes were enhanced. The inheritance was autosomal recessive.

Brown described autosomal dominant inheritance of progressive muscular atrophy in two New England families, Wetherbee and Farr. Known as the "Wetherbee ail," the disease was described in 1874 by Edward Wetherbee, a member of the family. The Farr family was reported on by William Osler in 1880. Magee described familial progressive bulbar-spinal muscular atrophy.

879. Mandell and Smith discussed *hereditary sensory radicular neuropathy* manifested by arthropathy (Charcot type), recurrent ulceration in the lower extremities, and signs of radicular sensory deficit in both the upper and the lower extremities, without any motor dysfunction.

Taylor studied a family in which five generations were affected by single or recurrent attacks of *mononeuritis* with a particular predilection for proximal brachial localization. The trait behaved as an autosomal dominant one with high penetrance. Clinically, the picture closely resembled serum neuritis, suggesting that the fundamental defect might be a genetic susceptibility to "hyperergic reactions."

Isaacs described a family with chronic hypertrophic polyneuropathy in which affected members developed paralysis of the extremities in cold weather.

880. Jervis described in detail the clinical, autopsy, and chemical features of 2 cases of infantile *metachromatic leukodystrophy* (Greenfield's disease). He pointed out that accumulation of sulfatides in demyelinated areas (and to a lesser extent in nerve cells and other tissues of the body) is characteristic. He suggested that it should be grouped with the lipidoses (a view subscribed to also by Norman, Urich, and Tingey) and be referred to as "sulfatidoses." In one kindred, Hagberg and colleagues observed 2 brothers and a male second cousin (related through males) with metachromatic leukodystrophy. Hariga described 2 brothers with leukoencephalopathy and metachromatic-staining material in the urine. Austin discussed the same disorder.

Poser discussed the classification and differential diagnosis of the diffuse scleroses of childhood.

881. Liu and Sylvester described 2 idiot brothers with *diffuse progressive encephalopathy* beginning before or about the time of birth and progressing with mental deterioration, epileptic fits, spasticity, paralysis, deafness, and blindness. Death occurred at 16 months and 38 months, respectively. The principal patho-

logic finding was paucity of nerve cells in the cortical gray matter, cerebellum, and substantia nigra. The picture did not agree exactly with any of the well-known types of encephalopathy.

Hariga described 2 children of a consanguineous marriage who showed clinical signs of infantile encephalopathy. Autopsy left open the possibility that congenital toxoplasmosis might be responsible. Martoni and Musiani considered probable examples of congenital toxoplasmosis in successive pregnancies.

Crome and Williams observed typical *multilocular encephalomalacia* at post-mortem examination in a one-month-old infant. A sibling, still living at age 6 with microcephaly, spastic diplegia, and idiocy, was thought to have the same disorder and a genetic basis was proposed.

882. Aronson, Valsamis, and Volk described 2 Negroes who represented typical instances of *infantile amaurotic familial idiocy*. They compared the disease in 88 non-Jewish children with that in 148 Jewish infants. Except that the gene is much more frequent in Jewish populations, there are no differences clinically or pathologically.

Harlem concluded that in the Spielmeyer-Vogt form of juvenile cerebro-retinal degeneration, vacuolization of leukocytes is a useful way to make an early diagnosis of the affected homozygote, but that it is of no use in the detection of heterozygotes. Terry and Korey studied cytoplasmic granules in the leukocytes in infantile amaurotic idiocy.

A. *B.*

Fig. 59.—The von Hippel-Lindau syndrome. V. B. (634120), a Negro man, was 39 years old at the time of onset of cerebellar signs and symptoms. Examination of the fundi through widely dilated pupils revealed a typical angioma at 4 o'clock in the right fundus 6 to 8 disc diameters from the disc. The mass was 3 to 4 disc diameters in size, elevated, and whitish, with dilated vessels about it.

The maternal grandfather died at the age of 45 years of paralysis. The mother died in 1916 at the age of 36 years. Because of the availability of both clinical and autopsy records on the mother, a precise diagnosis was possible in the son even before craniotomy. The mother had cerebellar manifestations resembling those of the son. Furthermore, there was a large yellowish white body projecting into the vitreous from the margin of the right optic disc. She died suddenly following a fit. Autopsy revealed, in the left cerebellar hemisphere, a cyst containing clear straw-colored fluid. Although von Hippel wrote before 1916, the syndrome did not receive wide or clear recognition until Lindau's classic paper was published in 1926.

***A*, The dilated vein draining the angioma is visible at 4 o'clock. *B*, The actual angioma.**

Fig. 60.—Cardiac involvement in Friedreich's ataxia.

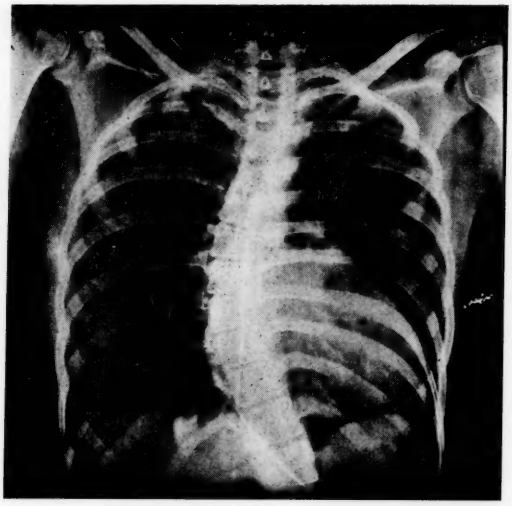


Fig. 60*A*.—Note the scoliosis and the cardiomegaly.

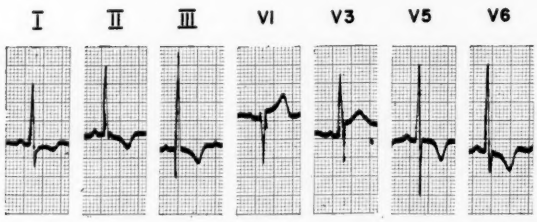
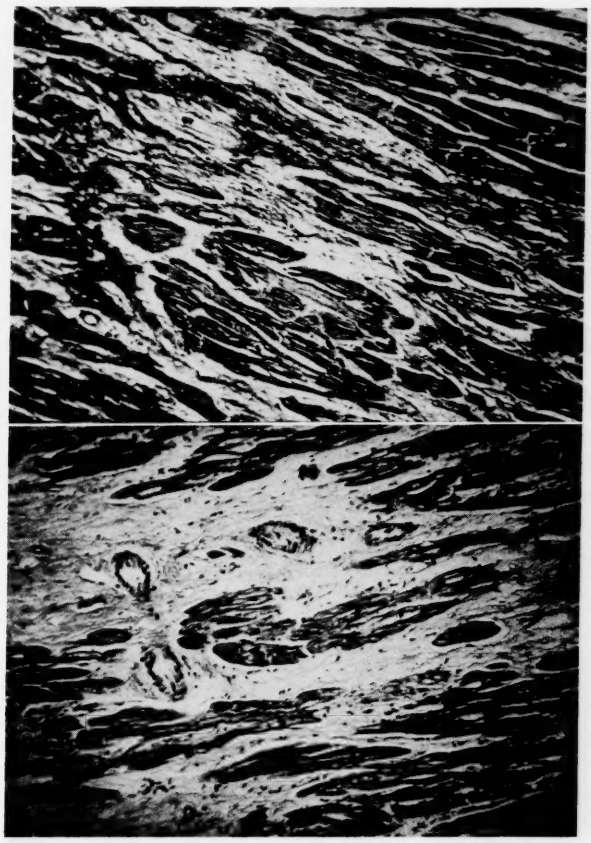


Fig. 60*B*.—Pronounced, although nonspecific, T wave changes.

883. A 9-year-old white boy with *Seitelberger's spastic amaurotic axonal idiocy* was described by Nakai, Landing, and Schubert. Other reports indicate a genetic basis, but this is apparently the first case recognized in a male. The patient had hypoplastic anemia from 8 to 26 months of age and later developed neurologic manifestations of cerebellar and brain stem dysfunction. At autopsy, the central nervous system showed deposition of chromolipid pigment in the basal nuclei and brain stem, degeneration and gliosis of the dorsal portions of the brain stem and spinal cord, and segmental hyalin swelling of axons, especially in the cerebellum. The visceral manifestations are of great interest: severe testicular atrophy, nodular change in the adrenal cortex, and renal cortical fibrosis with deposition in the renal tubule cells (especially those of the loops of Henle) of chromolipid pigment similar to that in the brain. The possibility of diagnosis by renal biopsy or by examination of the urinary sediment was suggested by these workers.

C.



D.

Fig. 60*C* and 60*D*.—The diffuse interstitial fibrosis found at autopsy.

884. Chandler, Reed, and Russell reviewed the behavior of *Huntington's chorea* in a large series of cases in Michigan. (See Fig. 61 for data on the age of onset.) Myrianthopoulos and Rowley described female monozygotic twins concordant for Huntington's chorea, from which their father had died.

885. In four generations of a family they previously reported (¶584), Zeman, Kaelbling, and Pasamanick studied the formes frustes of *dystonia musculorum deformans*. Asynergy, hyperkinesia, postural abnormalities, contracture deformities, and possibly mental defect were mild manifestations of the disease, which is inherited as an autosomal dominant trait. Ribera and Cooper discussed the natural history of the disorder.

886. Larsson and Sjögren did a thorough study of *hereditary essential tremor* in a parish of Sweden. In all, 210 tremor cases were ascertained. The age

of onset was on the average about 50 years and was somewhat later for women than for men. The age of onset showed high intrafamilial correlation. "Anticipation" was not observed. Fine rapid tremor of the hands is usually the first symptom. Tremor of the arms, tongue (with dysarthria), head, legs, and trunk develops later, usually in the order listed. Mild extrapyramidal symptoms in the form of rigidity and stiffness of gait occurred frequently, but the clinical picture was easily distinguishable from parkinsonism. Mental deterioration was not a feature. With 2 exceptions, all 210 cases could be traced back to four ancestral couples. The inheritance was autosomal dominant. From observation of about 15 presumed homozygous individuals, it was concluded that there is no difference from the disease in heterozygotes. It was estimated that more than 9 per cent of males and 6 to 6.5 per cent of females of the parish carry the gene for essential tremor. The authors could find no reason to suspect selective fertility, selective mortality, or assortative mating as factors in the high gene frequency observed. Rather, chance variations that occurred when the population was small—about 150 persons in the late 1700's—seem to have been responsible.

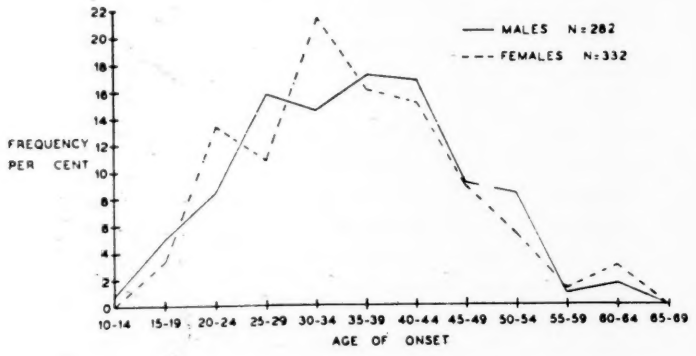


Fig. 61.—Huntington's chorea. Frequency distribution of age of onset. (From Chandler, J. H., Reed, T. E., and Russell, N. D.: Neurology 10:148, 1960; published by the American Academy of Neurology.) Similar data useful in genetic counseling were provided by Landzettel and coauthors (Acta genet., 1959) on the basis of 762 patients and plotted by Stern in his textbook (his Fig. 123) (¶657).

887. Convulsive disorders. Badr El-Din described a familial convulsive disorder with the unusual feature of apparent onset of convulsions in the fifth or sixth month of intrauterine life. The disease, possibly a "new" one, was observed among the children of 3 brothers who married 3 sisters. Physical and mental retardation, generalized hypertonus, reflex myoclonus, convulsions, and death in the first years were features. No postmortem data were available.

Metrakos and Metrakos discussed the methodologic problems in investigating the role of heredity in epilepsy. Brendemoen found a possible excess of blood group A in patients with cryptogenic epilepsy.

Noad and Lance observed *myoclonic epilepsy* in association with cerebellar ataxia in several children of first cousins once removed. Linkage with blood groups was sought, but "no suggestion of linkage" was found.

Yoss and Daly wrote on *narcolepsy.*

888. Rosenbaum described cases of *familial hemiplegic migraine.* The mechanism is thought to be vasoconstriction initially, followed by focal edema, which is responsible for the neurologic manifestations.

889. The intellect. Maxwell and Pilliner contributed to the genetics of *intelligence.*

Paine reviewed familial biochemically determined *mental retardation* in children. Since all hereditary diseases undoubtedly have a biochemical basis which will, we hope, be understood in due course, the author might better have worded his title to indicate those types of mental defect in which a biochemical defect has to date been demonstrated or suspected on good basis. Table XVII gives Paine's classification. The legitimacy of including infantile hypercalcemia and possibly some of the others is questionable.

Cowie discussed the classification of *microcephaly.* True microcephaly is the term used for the clear-cut genetic variety inherited as an autosomal recessive characteristic. It seems to be well established that x-ray exposure of the mother in early pregnancy may result in microcephaly.

Illingworth and Woods found that of 729 mentally retarded children without cerebral palsy, 3.8 per cent were twins. Of 651 children with cerebral palsy, 8.4 per cent were twins.

890. Oettlé, Rabinowitz, and Seftel described germinal aplasia of the testis in a case of full-blown *Laurence-Moon-Bardet-Biedl syndrome.* Normal pituitary function was evidenced by adult Sertoli cells and Leydig cells in the testis and by high-normal follicle-stimulating hormone. A case of this syndrome in association with the true chromatin-positive Klinefelter syndrome (with XXY complement) has been studied by the reviewers.

891. Mongolism. Warkany summarized a symposium on Mongolism held in the fall of 1959. The participants discussed problems such as the familial aggregation for Mongolism, the significance of microsymptoms in relatives of Mongoloid idiots, the possible cytogenetic mechanism for the development of this trisomy, and the theoretic implications with regard to gene action.

Kratter emphasized the high frequency of endocrine disorders in the mothers of patients with Mongolism. A metabolic disorder in the mother may yet prove to be related to the chromosomal aberration. Tsubakihara also studied the mothers of patients.

Dunston, Carter, and Huntley studied 44 Mongoloid children who had attended primary schools, private schools, and special schools for the educably subnormal. The highest IQ on the Terman-Merrill test was 68. When related to a total group of 390 Mongolian idiots from whom the 44 were selected, it was estimated that 6 to 7 per cent have an IQ of 45 and over, 1 to 2 per cent 55 and over. No association between degree of somatic stigmata and IQ was observed.

Mullins, Estrada, and Gready described the pregnancy of a Negro female Mongoloid idiot. At 22 months of age, the offspring seemed normal in physical and mental development. "Also perplexing," they commented, "is the fact that

TABLE XVII. FAMILIAL METABOLIC DISEASES ASSOCIATED WITH MENTAL RETARDATION*

Diseases of Carbohydrate Metabolism

Galactosemia
Sucrosuria (may be coincidental)
Glycogen storage disease
Gargoylism (mucopolysaccharide storage)
Spontaneous hypoglycemia (with deficient beta cells of pancreas)

Diseases of Lipid Metabolism

Progressive leukoencephalopathies (Schilder, Krabbe, Scholz, Greenfield, metachromatic, Bâlo, Merzbacher-Pelizaeus, and rarer demyelinations)
Progressive lipidoses of gray matter (Tay-Sachs, Bielschowsky, Kufs, Spielmeyer-Vogt, Niemann-Pick, Gaucher)
Hepatomegaly and mental retardation, with increased triglycerides in blood (Bigler and coauthors)

Diseases of Protein Metabolism

Phenylketonuria
Argininosuccinicaciduria (Allan and coauthors and Westall)
Cystathioninuria (Harris)
Maple syrup urine disease (Menkes)
Hartnup disease (Baron and coauthors)
Cystinuria (some cases—Berry)
Oasthouse urine disease (Smith and Strang)
Glycinuria (Childs and Cooke)
Pseudohypertrophic muscular dystrophy (sometimes retarded mentally)

Diseases of Calcium Metabolism

Infantile hypercalcemia (severe form)
Pseudohypoparathyroidism
Cerebral calcification epilepsy? (Geyelin and Penfield)

Other Diseases

Wilson's disease
Congenital renal tubular acidosis (de Toni-Fanconi syndrome)
Buphthalmos and decreased renal ammonia production (Lowe and coauthors)
Early convulsions, increased spinal fluid protein, and aminoaciduria (Joseph and coauthors)
Sex-linked microcephaly, spastic diplegia, and aminoaciduria (new)
Pyridoxine dependency
Some cases of hypsarrhythmia?

*From Paine, R. S.: New England J. Med. 262:658, 1960.

this mongoloid female, whose husband is deficient mentally and many years older than she, was able to produce a perfectly normal infant." The observation is noteworthy but not perplexing.

Brothwell presented evidence to support the view that a skull exhumed in England from a late Saxon burial ground was from a Mongoloid individual.

Alwyn Smith re-examined data on Mongolism in twins in the literature and concluded that the reports are consistent with invariable concordance of monozygotic pairs.

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Abrahamsen observed the combination of Mongolism and leukemia. Fischler and Farchy detected congenital leukemia in a 2-day-old Mongoloid infant. Davis and Korst presented the case of a 3-year-old boy with Mongolism and subacute granulocytic leukemia.

Nickey described a Mongoloid child with thyrotoxicosis—probably the fourth case in the English literature.

Priest and also O'Brien, Haake, and Braid confirmed earlier findings (¶591) of the exaggerated responsiveness of Mongoloid idiots to atropine, using pupillary dilatation as the measure of response. Furthermore, increased response to hydroxyamphetamine was observed (Priest). O'Brien, Haake, and Braid found no similar sensitivity of Mongoloid idiots to homatropine. There was no difference in any of the responses after administration of reserpine intramuscularly.

Toolan found that hamsters injected at birth with fractions or cell-free filtrates of transplantable human tumor cells, as well as certain tissues derived from human beings and rats carrying spontaneous cancers, developed a clinical picture suggestive of Mongoloid idiocy in man. Slant eyes or exophthalmos, protruding tongue, flat face, abnormal teeth, placidity, dwarfism, and other features were displayed. The author concluded that the syndrome is quite different from the "runting syndrome" produced in rats and mice. Furthermore, the Mongoloid syndrome was not produced in rats and mice by similar injections. Seemingly, a phenocopy of the human disease has been produced. It is doubtful that the mechanism of production of the human disease is elucidated by these observations.

892. Richards reported a case of *Sjögren-Larsson syndrome* (congenital ichthyosis, spastic diplegia, and mental deficiency) in the 13-year-old daughter of first cousins. Williams and Tana observed a brother and sister with the same syndrome. The entire family (3 siblings and both parents) showed aminoaciduria. The skin lesion is histologically similar to congenital ichthyoform erythroderma.

893. Zu Rhein, Eichman, and Puletti described familial idiocy, with spongy degeneration, of the van Bogaert-Bertrand type.

Others: 894. Myrianthopoulos and Mackay studied fifty-four pairs of twins in whom at least one of each pair had *multiple sclerosis*. The frequency in their relatives was twenty to thirty-two times higher than in the general population. The analysis of the data on the families led them to the conclusion that the findings are consistent with autosomal recessive inheritance assuming about 43 per cent penetrance in persons homozygous for the mutant gene. They properly emphasize, however, that consistency with the hypothesis is *not* proof. They refer to the likelihood that environmental factors collaborate with genetic ones. The environmental factor most clearly demonstrated is something related to latitude. Multiple sclerosis is more prevalent in cold and northern climates than in warm and southern ones.

895. Jager and colleagues described a case of *Refsum's syndrome:* retinitis pigmentosa, ophthalmoplegia, ataxia, deafness, and heart block. Protein in the

cerebrospinal fluid was increased. The patient, aged 13, died of the cardiac disturbance. Autopsy revealed no change in the central nervous system or peripheral nerves. The disorder, described by Refsum, contemporary Oslo neurologist, behaves usually as an autosomal recessive trait.

896. Gillespie and Perucca described a case of *congenital generalized indifference to pain* (congenital analgesia), a condition first described by Ford and Wilkins in 1938. There were no similar cases in the family and no consanguinity. Seemingly familial cases have not been reported. Baxter and Olszewski found no anatomic change to account for congenital *universal* insensitivity to pain in a 28-year-old patient who interestingly had Charcot joints.

Bloom and Moynahan found that in a family in which many members had hereditary hemorrhagic telangiectasia, 2 affected sisters had fits and a third had an abnormal electroencephalogram. Intracranial telangiectases were postulated. The father and paternal grandmother had telangiectases.

Ullrich and Sugar reported on four families in each of which 2 members had cerebral aneurysms. (See ¶937.) We have observed a 34-year-old man and his 13-year-old daughter, both of whom died of intracranial "berry" aneurysm.

897. Dobzhansky drew attention to a eugenic policy, apparently without precedent anywhere, which has been announced by the Australian administration of the Territory of New Guinea. The measure, genetic quarantine, affects the Fore tribe, which numbers about 30,000 persons in an area of approximately 884 square miles. Migration will be prohibited. The use of Fore men, many of whom may be carriers of kuru, as laborers in other areas will be discontinued. Economic improvement of the Fores will be attempted, and studies of the disease will continue. Kuru must be unique among human diseases in its behavior as a recessive in males and dominant in females (assuming that the prevailing genetic hypothesis is correct). Bennett reviewed the subject of kuru.

Parry discussed *scrapie*, a transmissible, hereditary multisystem disease of sheep. The transmissibility by intracerebral inoculation seems unquestioned. The transmissible agent is unusually resistant to heat and chemical agents. No immunoserologic changes have been demonstrated. The familial incidence is consistent with an autosomal recessive trait; almost all offspring of 2 affected parents can be expected to develop the disease.

898. Psychiatric disorders. Böök expressed a pessimistic outlook on the genetic usefulness of traditional family and population studies of *mental illness.* See also the contribution of Schwartz.

Rosenthal pointed out that the "confusion of ego identity" theory of schizophrenia could account for higher concordance in monozygotic than in dizygotic twins but that a higher frequency of schizophrenia in twins and a higher frequency in monozygotic than in dizygotic twins are implied. A study stimulated by these considerations produced no evidence that schizophrenia or mental illness requiring hospitalization is any more frequent in twins than in nontwins or in monozygotic than in dizygotic twins.

899. Neurosis in families. Ehrenwald, in a study based on 14 members of a family in four generations and supplemented by three more families, developed the concept of contagion with spread of "sick" interpersonal attitudes vertically and horizontally in pedigrees. That the spread in families is facilitated by hereditary factors was mentioned as a possibility.

900. Swanson reported on *suicide* in a pair of separated identical twins. We have known of suicide in grandfather, son, and grandson.

XX. SKELETAL SYSTEM

901. Reviews. Silverman and Currarino provided a useful review of roentgenologically demonstrable skeletal changes in hereditary metabolic disorders of childhood: vitamin D–refractory rickets, cystinosis, Lowe's syndrome hypophosphatasia, pseudohypoparathyroidism, hypothyroidism, the adrenogenital syndrome, and others. Some of the points emphasized were the inadequacy of available standards for dental age and the changes in dental age in the disorders under discussion, the existence of several varieties of vitamin D–refractory rickets, the occurrence of craniostenosis in hypophosphatasia, vitamin D–refractory rickets, and other disorders, and beaking of lumbar vertebrae in hypothyroidism (simulating that in gargoylism). See also Wiedeman's monograph.

Lane reviewed and illustrated the roentgenographic manifestations of what he termed cartilaginous dysplasias: classic achondroplasia, Hurler's syndrome, Morquio's syndrome, Léri's pleonosteosis (with report of another American case of this rare syndrome, ¶523), multiple epiphyseal dysplasia, Ollier's dyschondroplasia (multiple enchondromatosis), multiple exostoses, and dysplasia epiphysialis punctata. The last condition is also called chondrodystrophia calcificans congenita and stippled epiphyses. Pathologically marked vascularization of the epiphyseal cartilage is characteristic. Lane claims it is not genetic.

902. Vesell described a syndrome of *symphalangism* (absent proximal interphalangeal joint), strabismus, and hearing loss in a mother and daughter. The digital defect was identical to that traced back fourteen generations to John Talbot, first Earl of Shrewsbury, born in 1390 (Drinkwater, 1917). In this and other pedigrees, it has behaved as an autosomal dominant trait. Whether the strabismus and deafness were due to a separate mutation occurring as a coincidence in this mother and daughter or whether a unique mutation resulted in all three manifestations is not clear. Vesell referred to the excursion into genetics of neurosurgeon Harvey Cushing: "Hereditary Anchylosis of Proximal Phalangeal Joints (Symphalangism)" (Genetics 1:90, 1916). Rather clearly, Cushing's paper was published at the instigation of William E. Castle, a colleague in Harvard University, who was an editor of *Genetics*. Appearing in the first issue of the first volume, it was a companion to the important paper of Calvin Bridges entitled "Non-disjunction as Proof of the Chromosome Theory of Heredity." (See Fig. 62 for an example of symphalangism.)

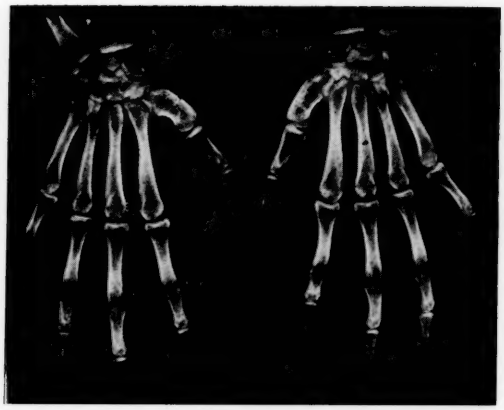


Fig. 62.—Symphalangism with carpal and tarsal fusions in grandmother, father, and 4 of 7 children. The father died suddenly at the age of 45 years. The mother had symphalangism. A feature which is of note is the progressive postnatal nature of the synostosis in this family. (In fibrodysplasia ossificans progressiva, the synostotic process resulting in monophalangy of the toe and thumb is often observed to proceed in postnatal life.) The bones of the tarsus and carpus are either totally or partially fused in all cases. The x-ray shown here is of a 23-year-old woman, a member of the third affected generation. The changes are completely typical of those reported in the literature, and no special comment is required. (Courtesy of Dr. Cristóbal Vélez, Lima, Peru.)

Sugiura and Inagaki described a Japanese kindred in which symphalangism was associated with fusion of the carpal and tarsal bones and was inherited as an autosomal dominant trait as in Caucasian families.

903. Mériel and colleagues described 2 cases of the *nail-patella syndrome* (osteoonychodystrophy). One patient had an abnormality of the meniscal cartilages. They suggested that an exaggerated "fish hook" curvature of the sacrum deserves inclusion among the skeletal features of the syndrome. Papadimitriou reported on a family with the nail-patella syndrome, or, as he chose to title it, hereditary arthroosteoonychodysplasia. His pedigree corroborated dominant inheritance. Linkage data were not collected.

Stevenson and Jennings brought up to date a pedigree of ectrodactyly ("lobster claw" or "split foot") described first by Karl Pearson in 1908. An excess of affected over unaffected offspring as compared with the ratio expected on a single dominant gene hypothesis was maintained. The excess was apparently determined entirely by a marked preponderance of affected sons of affected fathers. Other large pedigrees of this condition show the same phenomenon. These workers suggested germinal selection as the most likely explanation. (See ¶848 for a discussion of anomalous segregation in aniridia.)

904. Dunn described coxa plana (*Legg-Perthes disease*) in monozygotic male twins. The left hip only was involved in both.

905. Arthrogryposis multiplex congenita has not previously been considered hereditary to an important extent. However, Frischknecht, Bianchi, and

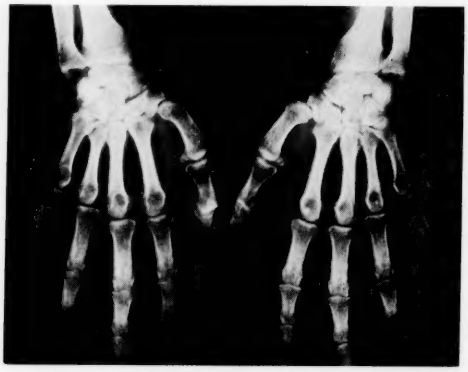
Pilleri reported it in 3 siblings and described the pathologic findings: degeneration of anterior and lateral bundles of the cord, resembling that in amyotrophic lateral sclerosis, and almost complete lack of Betz cells in the gigantopyramidal layers of the motor areas, the last being a finding not previously described. They suggested neuroarthromyodysplasia as a designation.

906. Barber described "an unusual form of *familial osteodystrophy*" in 4 brothers varying in age from 39 to 54 years. All were 56 inches or less in height, with particularly short trunks and degenerative disease of the hip joints. All other members of the family were normal; one affected brother had 2 normal children, and one had 7 normal children. From the entire description, the Morquio-Brailsford syndrome seems most likely. However, Brailsford reviewed the x-rays and concluded that the disorder is a form of osteochondrodystrophy not previously described. It seems possible to the reviewers that the Morquio-Brailsford syndrome in adulthood may be sufficiently different in its radiographic appearance that it is not recognized as the same disorder which the orthopedist deals with in children. Barber later pointed out a similarity of his cases to those described by Maroteaux, Lamy, and Bernard (1957) as "late spondyloepiphyseal dysplasia" and those reported yet earlier by Nilsonne (1927), Jacobsen (1939), and Volhard and Drigalsky (1937). There emerges the delineation of a condition characterized by arrest of development of the spinal column between the ages of 10 and 14 years occurring only in males and probably inherited as a sex-linked recessive trait.

Tanaka, Nemoto, and Sujaku described typical Morquio syndrome in a Japanese boy. A defect of dental enamel was present. The child was the offspring of a first cousin marriage. Many members of the family were examined; a number,

Fig. 63.—A phenocopy: "bound feet" in a Chinese woman. The changes shown in these radiographic views of the feet of a 65-year-old woman reared in the vicinity of Canton, China, simulate those seen in the feet in certain of the dysostoses, e.g., that discussed by Singleton, Daeschner, and Teng.

Fig. 64.—Multiple epiphyseal dysplasia in white father and son. The changes in the father taken alone might be difficult to interpret. Multiple epiphyseal dysplasia is a hereditary basis for precocious and severe osteoarthrosis, especially of the hips. Furthermore, because of short stature, children with multiple epiphyseal dysplasia may present to the pediatric endocrinologist as having a growth problem. (Courtesy of Dr. R. A. Milch.)



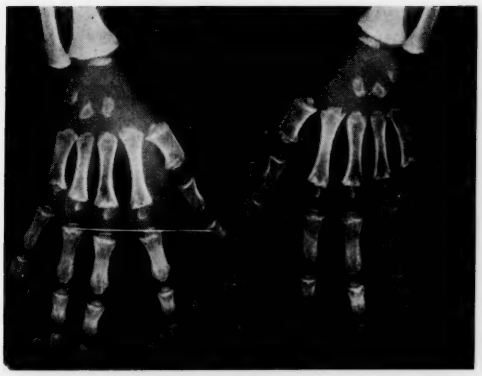
A.

B.

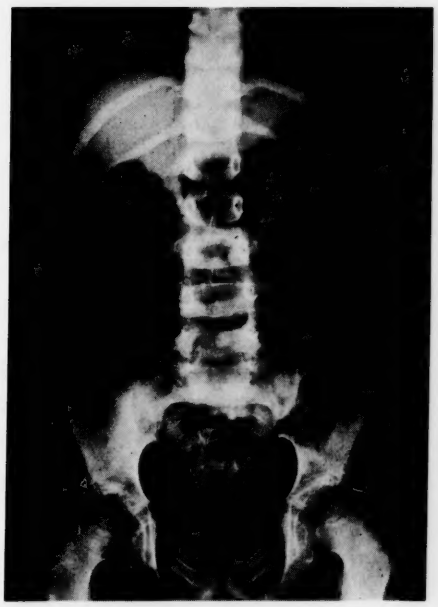
Figs. 64*A* and 64*B*.—H. W. C., Sr., age 41 years, is short of stature, has stubby fingers, and has marked limitation of motion and pain in the hips. A brother is said also to have hip trouble.

including the father, had mild skeletal anomalies which were interpreted as indicative of heterozygote state: hyperextensibility of finger and toes and shorter, wider hand bones "than one might expect."

Von Noorden, Zellweger, and Ponseti described 2 brothers with a syndrome consisting of the skeletal features of the *Morquio syndrome* and *cloudy cornea* as in the Hurler syndrome. They found 15 similar cases in the literature. They suggested the designation Morquio-Ullrich. "The Ullrich type of Morquio



C.



D.

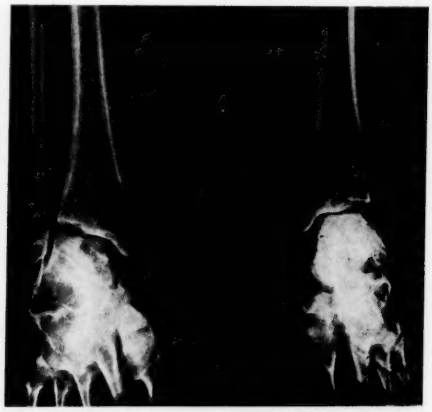
Figs. 64*C* and 64*D*.—The son, H. W. C., Jr., age 10 years, is also short of stature and has typical radiologic changes of multiple epiphyseal dysplasia.

syndrome" or simply "the Ullrich syndrome" might be less confusing. The patients showed a semicrouching position, sternal deformity, genu varum, loosejointedness, deafness, malformation of the angle of the anterior chamber by gonioscopy, Reilly granules in the peripheral blood cells, Alcian blue–positive granules in the cells of bone, cartilage, and bone marrow, and, finally, increased mucopolysaccharides in the urine, but in amount less than in the usual case of the Hurler syndrome.

907. Schwarz discussed a condition he called *craniometaphyseal dysplasia*, a familial disorder with frontal bossing, knock-knees, wide metaphyseal ends of the bones, faulty dentition, hyperostosis of craniofacial bones, cranial nerve involvement, scoliosis, and bowing of long bones. An 18-year-old man who was for some time thought to have osteogenesis imperfecta was described. The condition seems to be inherited as an autosomal recessive trait.

908. Daeschner and colleagues described father and son with *metaphyseal dysostosis.*

Fig. 65.—Multiple epiphyseal dysplasia in Negro mother and daughter.



A.

B.

Fig. 65*A* and 65*B*.—E. J., age 34 years, shows the slope of the distal end of the tibia (*A*) which may be one of the few clues to the diagnosis of epiphyseal dysplasia in the adult. There are symptoms and radiologic (*B*) evidence of precocious osteoarthrosis of the hips.

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Singleton, Daeschner, and Teng reported a form of *peripheral dysostosis* limited essentially to the tubular bones of the hands and feet. (See Fig. 63 for an interesting phenocopy.)

Leeds described father and son with *epiphyseal dysplasia multiplex* (Figs. 64 and 65). The father had severe osteoarthrosis of the hips. The author pointed out that the diagnosis in the adult is aided by the changes in the distal epiphyseal ossification center of the tibia. A deficiency in the lateral part of the epiphysis seen in childhood results in a slanting of the distal end of the tibia in the adult.

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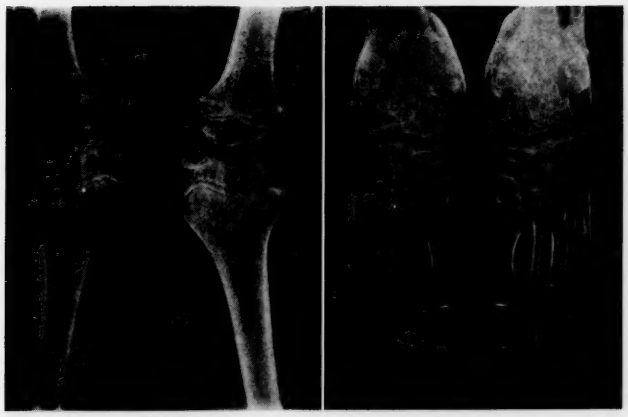
C.



D. *E.*

Figs. 65*C*, 65*D*, and 65*E*.—The daughter, M. J., age 11 years, the proband, presented with knock-knees and shows marked changes in many epiphyseal cartilages. She is below average for stature.

909. Allansmith and Senz reviewed 54 cases of *chondrodystrophia congenita punctata* from the literature and added another. Dwarfing, contractures, mental retardation, cataracts, and skin changes are among the characteristic findings in addition to those in the skeleton (see Fig. 66). Many die in the first year of life. Whether survival to adulthood ever occurs and, if so, what the clinical picture is, no one seems to know. The occurrence of multiple affected siblings suggests a genetic basis.

910. Engfeldt and colleagues analyzed the roentgenologic and pathologic changes in *osteopetrosis*. The "bone within a bone" appearance was well illustrated and explained by their findings. (See Figs. 67 and 68 for examples of two types of osteopetrosis.) A familial instance of monostotic osteopetrosis was reported by Sfikakis and Matsas.

911. Knight reported 3 brothers with sarcomatous changes complicating *diaphyseal aclasis* (multiple exostoses). He found 26 cases of this complication in the literature but found no other instance of more than one case in the same family. We have seen two families with multiple members affected by this complication (Fig. 69).

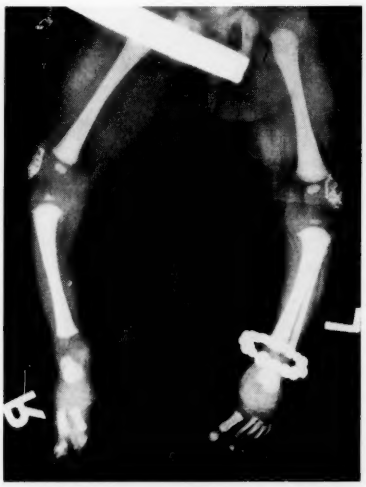


Fig. 66.—Chondrodystrophia calcificans congenita. X-ray of a white female infant (B20225) who died at the age of 21 days. The prognosis is in general poor. This was a first child. Other anomalies included mild webbing of the neck, complete flaccidity, delayed ossification of the skull bones, and abnormal pattern of ossification in the ileum. The child was thought to be cyanotic, but there were no other signs of congenital heart disease. Permission for autopsy was denied. One sibling is living and well. The parents were not related.

912. Cases of *Ollier's disease* (multiple congenital enchondromatosis and dyschondroplasia) were reported (Cabot case).

Johnson, Webster, and Sippy described a case of *Maffucci's syndrome* (dyschondroplasia with hemangiomata) in which two separate chondrosarcomas had occurred and the patient died from carcinoma of the pancreas with widespread

Fig. 67.—Osteopetrosis, adult type. In 1922 the late Dr. Ralph K. Ghormley described "a case of congenital osteosclerosis" in a boy then 9 years old (Bull. Johns Hopkins Hosp. 33:444). The father and uncle were similarly affected. The uncle, who subsequently died in his seventies, had much trouble with osteomyelitis of the jaw. The father was a strong man. He broke his leg following trauma. He died at the age of 52 after surgical operation for peptic ulcer. The proband sustained fractures whenever he engaged in rough sports. At age 32 he began to have trouble with osteomyelitis of the mandible. There was progressive stiffening of the hips. Despite his physical handicaps, the proband became an international authority in the field of dielectrics. At the age of 45 years he developed symptoms of a temporal lobe abscess and died from this 2 days later.

Fig. 67*A*.—Shown are the marked sclerotic changes in all bones and the defect in the mandible where surgical procedures for osteomyelitis were performed.

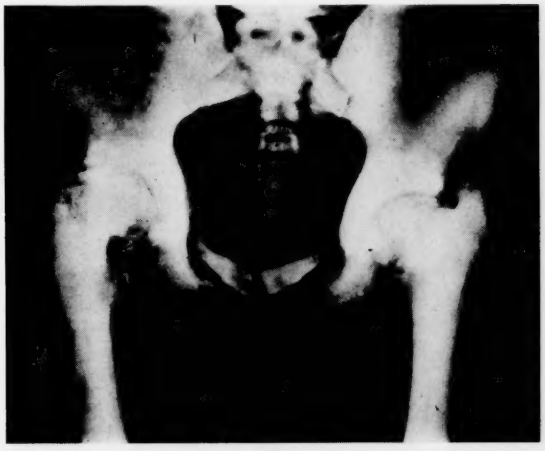


Fig. 67*B*.—Changes of secondary osteoarthrosis of the hips.

metastases. The authors pointed out that a familial incidence had apparently never been demonstrated. A chromosomal aberration should be sought. Probably not sufficient cases have been observed to exclude completely the possibility of transmission as a rare autosomal recessive trait. No statement was made as to whether the patient had children; the possibility of a rare dominant mutation cannot be evaluated. The author comes to a curious conclusion on the nature of the entity: "The syndrome is probably a congenital mesodermal dysplasia ["probably" is not necessary; "obviously" could have been used] which is not inherited but due to multiple defects in a single gene."

Ashenhurst described Maffucci's syndrome in a 60-year-old woman. The relatives, including a 30-year-old son, were all unaffected. The patient died of a primary intracranial neoplasm. The author stated that one other instance of primary brain tumor has been described (Carleton and coauthors, Quart. J. Med. 11:203, 1942). In addition, symptoms from intracranial extension of chondromata or chondrosarcomas of the skull have been described in many of these patients. We have observed an instance of the Maffucci syndrome in which death was due to ependymoma (Fig. 70). There appears to be a marked and possibly nonspecific tendency to malignancy in patients with this disorder.

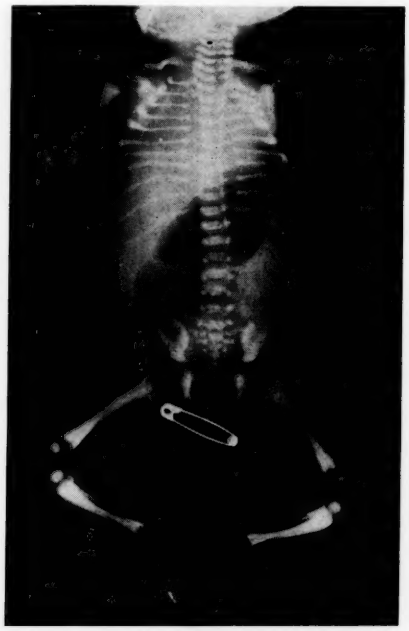


Fig. 68.—Osteopetrosis of the "malignant" infantile type, probably an autosomal recessive trait. A white male infant (A16696) died at 4 months. The clinical manifestations were rapid breathing and purpura. He was severely anemic and thrombocytopenic. WBC 46,000, with an increase in immature forms, was determined. X-rays (shown) revealed dense homogeneous bones without marrow cavity and with marked rachitic changes at the ends of the long bones. The heart was greatly enlarged. Autopsy revealed in addition to the bone changes of Albers-Schönberg disease and of rickets, extramedullary myeloid infiltration in many organs. One sibling died at 4 months, presumably of brain abscess. There are no other siblings. The parents are not known to be related. They are clinically normal.

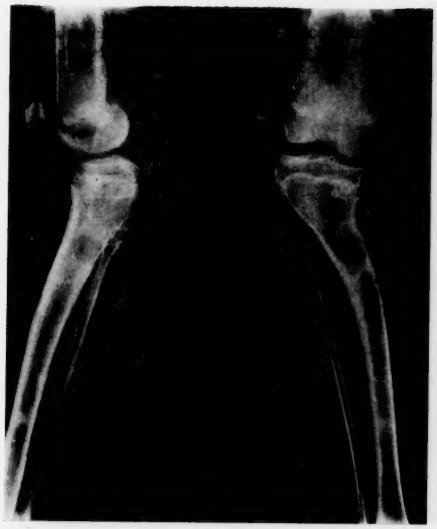


Fig. 69.—Multiple exostoses (diaphyseal aclasis). The disorder in this 13½-year-old child (M. H., 352724) and her younger sister goes back many generations in a family derived from Czechoslovakia. The grandfather of this patient died of sarcomatous degeneration of exostoses. The mother of this patient has recently had a chondrosarcoma removed from a rib. Another patient, a 42-year-old man, with sarcomatous degeneration in a rib exostosis has recently been observed. His daughter also has multiple exostoses.

913. Carter and Sweetnan studied the families of 97 patients with *recurrent dislocation* of the patella and of 40 with recurrent dislocation of the shoulder. Of the first group 10 and of the second 2 had a near relative with similar dislocation. Familial joint laxity, apparently transmitted as an autosomal dominant trait, was present in two of the first-mentioned ten families and in both of the two families with multiple members affected by recurrent dislocation of the shoulder. Familial joint laxity was found in 2 out of 20 patients with recurrent dislocation of the patella but no family history of similar dislocation. Whereas familial joint laxity may account for all instances of familial dislocation of the shoulder, such is not the case for familial recurrent dislocation of the patella.

914. Miscellaneous. Physiologic bowing of the legs, which is spontaneously corrected at the age of 2 to 3 years, may run in families (Sherman).

Trotter, Broman, and Peterson found the bones of Negro skeletons to be denser than those of Caucasian skeletons.

Garn and Rohmann discussed the variability in the order of ossification of the bony centers of the hand and wrist. Greulich discussed variations in the skeletal features of the hand and wrist as revealed by x-ray. The frequency of bifidity and related abnormalities of the ribs was determined by Martin in Samoans, on the basis of survey x-rays of the chest.

Mann, Bates, and Karnitschnig described a case of absence of the odontoid process. In most cases, the diagnosis was made by x-rays made when signs or

Fig. 70.—Ollier's enchondromatosis with fatal brain tumor. A. S. W. (429223), a white woman born in 1915, died in 1948 of an ependymoma of the brain. Osteochondromata were removed surgically at the age of 14 years. No further growth of the tumors occurred after puberty. The growths had first been noted at the age of 18 months. The tumors were confined to the extremities, particularly the hands and feet. There was a tumor in the right humerus. There was shortening of metacarpal bones and of the left tibia. "Epilepsy" began in 1944. Finally, by July, 1947, when marked bilateral papilledema had developed, the patient was admitted to the hospital and ependymoma was discovered on craniotomy. The tumor located in the right temporal lobe could not be totally resected. Known to us is another patient with Ollier's enchondromatosis who succumbed to brain tumor.

Fig. 70*A*.—Osteochondromata of the hands.

Fig. 70*B*.—Contrary to the suggestion of the photograph, there were no hemangiomata; this was not a case of Maffucci's syndrome.

symptoms of cervical dislocation or spinal cord compression developed after trauma. Family studies would be of interest.

Dr. Louise Pearce, who at the Rockefeller Institute studied a number of hereditary disorders in the rabbit, died on Aug. 9, 1959. Posthumously, her studies of hereditary premature senescence and of hereditary distal foreleg curvature were reported. The latter condition she concluded to be a chondrodystrophy localized to the distal epiphysis of the ulnar bones and to be transmitted as a simple recessive character.

XXI. SKIN AND OTHER INTEGUMENTAL STRUCTURES

915. Wheeler, Cawley, and Whitmore observed *hydroa aestivale* (manifested by a papulovesicular eruption, pigmentary change, and scarring of exposed skin surfaces) in both of 12-year-old white identical male twins. Porphyrinuria was absent in both the twins and their parents. Hydroa aestivale probably has multiple causes of which porphyria is only one. Langhof described cases of familial light urticaria.

916. Gorlin and Anderson, in studying *incontinentia pigmenti* (the Block-Sulzberger syndrome), concluded that there are characteristic dental changes. A familial condition, incontinentia pigmenti occurs predominantly in females. The genetics is probably complex. A systematic analysis is desirable.

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917. Bloom suggested that *acrodermatitis enteropathica* may be an inborn error of metabolism inherited as an autosomal recessive trait and involving a defect in intestinal digestion and/or absorption.

918. Graham, Schafer, and Helwig described *Fox-Fordyce disease* in male identical twins. A distinctive pruritic papular eruption was present in the axillae and around the nipples.

919. From Egypt, Awwaad and El Essawy described 2 brothers with *anhidrotic ectodermal dysplasia* of which the inheritance is usually sex-linked recessive.

920. Luce and Bean discussed *turban tumors* and mentioned the familial nature.

921. Berlyne and Berlyne described a family with "*blue-rubber-bleb*" *nevus disease* (cavernous hemangiomatosis) in five generations of a family. The skin lesions spared the face and fingers, thus differing from Osler-Rendu-Weber disease. The lesions sometimes occurred in the colon, causing anemia from bleeding into the stools. Theirs apparently is the first genetic investigation. The inheritance appeared to be straightforward autosomal dominant.

922. Forbes and Robson described 2 sisters and a brother with *recurrent orogenital ulceration.* The relation to the "triple symptom complex" of Behçet (recurrent oral and genital ulceration with iritis and hypopyon) was discussed. Herpes virus was not recovered, but significant titers by herpes neutralization tests were found in 2 of the 3 siblings. One had discoid lupus erythematosus. The other 2 had elevated sedimentation rates and possibly elevated levels of γ globulin.

923. Saúl described 2 sisters with erythematous scaly plaques, of geographic outlines and neat borders, which had been present almost since birth. The designation they suggested was *congenital familial erythrokeratoderma figurata* in plaques.

924. Franceschetti and Schnyder concluded that ***keratosis palmoplantaris*** limited to the palms and soles is transmitted as an autosomal dominant trait. A recessive form of the disease is more severe and is accompanied by other ectodermal changes. Heirli-Forrer described families with the dominant form. Presumably, the disorder discussed is the same as that called tylosis by Howel-Evans and colleagues, who pointed out the occurrence of carcinoma of the esophagus as a complication (¶120) and also indicated that in the form inherited as a dominant trait there is heterogeneity, since in some families esophageal carcinoma is not a complication.

925. In a triracial isolate in North Carolina, Witkop and colleagues found *benign intraepithelial dyskeratosis* of conjunctiva and oral mucous membrane in at least 83 persons. The oral lesion, which grossly resembles leukoplakia, is not precancerous. The eye lesions resemble pterygia. The only symptoms are produced by the spread of the eye lesion over the cornea, with production of blindness. Characteristic dyskeratotic lesions were found in oral and eye scrapings. The syndrome was transmitted as a highly penetrant (97 per cent) autosomal dominant trait and had little effect on reproductive fitness.

926. Roberts and colleagues described 3 cases of *epidermolysis bullosa letalis* in branches of an Acadian French family from an area in Nova Scotia with much inbreeding. The infants were born with bullous lesions and died at 20, 24, and 42 days, respectively, despite meticulous nursing care, antibiotics, corticosteroids, and increased dietary protein. No abnormality was demonstrable histologically, except in the skin. Loss of serum protein and electrolytes and dermal sepsis seemed to have been responsible for death. See also Ilič and Stevanovič.

927. Medansky and Fox described *hereditary leukonykia totalis* in 14 members of five generations of a family. The genetics of *koilonychia* ("spoon nails") was studied by Handa and colleagues.

928. Albright described *multiple lipomatosis* in Holstein-Friesian cattle. He concluded it was "inherited as a Mendelian dominant with incomplete penetrance, similar to the condition found in humans." However, the pedigree shown is more suggestive of recessive inheritance. Lipomata were first observed at the age of 3½ years and progressed markedly with advancing age.

XXII. TEETH

929. Reviews. Witkop published a review entitled "Dental Genetics 1959" organized along lines similar to this series. Krogman provided a superb review in an article entitled "Oral Structures Genetically and Anthropologically Considered." Its scope is too broad to permit review of its contents here. It will undoubtedly be a useful source to workers in this area for many years to come.

Coining a term, Gorlin and Chaudhry discussed some unusual "stomadromes"—symptom complexes with one or more oral components. In *pachonychia congenita*, transmitted as a simple dominant trait, dystrophy of the nails, hyperkeratosis of the palms and soles, follicular keratosis, and hyperhidrosis are associated with white, furred tongue. Epidermolysis bullosa congenita, the Turner syndrome, and multiple telangiectasia were also discussed.

930. Gorlin and Goltz described a hereditary syndrome consisting of multiple nevoid basal cell epitheliomas, cysts of the mandible, and bifid ribs. The inheritance appeared to be autosomal dominant with reduced penetrance.

McKelvey, Albright, and Prazak described what is undoubtedly the same syndrome: multiple benign epithelial cysts of the mandible and maxilla and concurrent trichoepithelioma (epithelioma adenoides cysticum) of the face and chest. The father and 2 brothers likewise had cystic lesions of the jaws. Skin lesions were described only in the proband. The bone condition is an entity separate from multilocular cystic disease of the jaws, or "cherubism."

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XXIII. URINARY SYSTEM

931. McCrory, Worthen, and Holliday separately discussed various aspects of disease of the renal tubule including hereditary defects. Leonardi, Ruol, and Munari studied the morphologic aspects of renal glycosuria.

Lowe discussed the *oculocerebrorenal syndrome* which bears his name (¶'s 197, 629). All patients have been male. In several sibships, more than one have been affected; 3 were affected in one of Lowe's families. Maternal uncles have been affected in some instances. He concluded the inheritance is sex-linked recessive. McCance and colleagues described what appears to be a variant of this syndrome in 2 brothers. Cases were also described by Sacrez and colleagues and by Terslev.

932. Skjaeggestad described acute *glomerulonephritis* occurring simultaneously in 3 of 5 siblings, whereas the other 2 had slight transient proteinuria. Genetic predisposition cannot be definitely concluded but may participate (with the particular streptococcus) in the observed familial aggregation. Wallace and Jones described 3 siblings (2 male, one female), who died of glomerulonephritis. All three surviving siblings, both parents, and one grandparent on each side had excessive aminoaciduria. Brief report was given of a second family in which 2 children out of 3 died of pyelonephritis. There was no aminoaciduria in this family.

933. Broberger, Winberg, and Zetterström and also Ivemark, Ljungqvist, and Barry discussed *familial juvenile nephronophthisis* (¶283). The condition behaves as an autosomal recessive trait. Parental consanguinity was present in at least two of twelve reported families. There is reason to think that the heterozygotes can be detected. Since the patient remains in good general condition

with proteinuria, erythrocyturia, edema, and arterial hypertension absent until late, the diagnosis may long be overlooked. One feature throughout is the presence of polyuria and hypotonic urine. Since the glomerular filtration rate is reduced, the volume of urine never reaches that observed in diabetes insipidus. The disease appears to be an ascending tubular degeneration beginning in the distal tubule or loop of Henle.

934. Chappell and Kelsey described a family with hereditary *nephritis* and *deafness* in four generations. The disease was more severe in males than in females. The pedigree was not inconsistent with partial sex linkage (¶631). The mooted matter of possible partial sex linkage was discussed further by Graham and by Perkoff, Stephens, and Tyler.

935. In 1957 Wilansky and Schucher reported a 33-year-old woman with recurrent renal stones, hyperchloremic acidosis, alkaline urine, oxaluria, reduced ammonia excretion, and impaired compensation to the administration of ammonium chloride. Her father had died of kidney disease and was found to have renal calcification at autopsy. Her brother, killed in an automobile accident at the age of 20 years, likewise had calcified shrunken kidneys. In 1960 the same authors, in an article entitled "Familial Acidosis of Renal Tubular Origin," described studies in the 3 children of their original patient. All 3, ages 9, 6, and 2½ years, showed signs of the same renal tubular defect.

Huth, Webster, and Elkinton also studied the family of a patient in whom primary renal tubular acidosis was associated with nephrocalcinosis and nephrolithiasis. The father of the proband had unilateral nephrocalcinosis, staghorn calculus, and hydronephrosis; one brother and 3 children showed only depression of the serum carbon dioxide level. Two of the 3 children showed low or borderline hydrogen ion clearance. The authors analyzed 162 cases from the literature.

936. McGeown found familial aggregation for *renal stone.* The frequency of gallstones was not increased in these families. No relation to aminoaciduria or hypercalciuria was demonstrated, but there was a relationship to increased urinary excretion of phosphate.

937. Ditlefsen and Törjum described a family in which there were 15 verified and 2 suspected cases of *polycystic kidney.* Six of the patients suffered cerebral hemorrhage. In one of the 6, aneurysm of the middle cerebral artery was verified. The association between cystic kidneys and intracranial aneurysm is strengthened by this family report. From an uncontrolled study of polycystic kidney disease, Goldstein and Goldstein concluded that survival was considerably enhanced by the use of the surgical procedure devised by one of the writers 25 years ago (J. Urol. 34:536, 1935). By "nephrocutaneous anastomosis," the kidney is opened and brought to lie beneath the skin. The cysts can be drained percutaneously at intervals of 6 to 12 months or as indicated by pain or rising blood urea level. Nixon and colleagues described 3 cases of polycystic kidney with polycythemia.

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Jean Oliver, in an editorial, and Fetterman and Feldman, in a case report, discuss what they propose to call infantile *microcystic renal disease*. The nephrotic syndrome is present in many of these cases. A genetic basis is suggested by the sibship reported by Giles and colleagues (Arch. Dis. Childhood 32:167, 1957). Oliver feels the entity is clearly distinct from the familiar polycystic disease of adult life.

938. Bridge observed *horseshoe kidneys* in both of identical twins.

939. Brinton described a family with multiple cases of hypernephroma. Drivsholm described a case of polycythemia with metastatic hypernephroma. Gurney also studied cases of polycythemia with hypernephroma.

The following features of familial hypernephroma and of polycythemia in association with hypernephroma have impressed the reviewers:

1. Aside from hypernephroma, hemangioblastoma of the cerebellum of the type occurring in the *von Hippel-Lindau syndrome* is the tumor most frequently responsible (Ward, Foltz, and Knapp, 1952).

2. Polycythemia occurs in persons with the von Hippel-Lindau syndrome (Cramer and Kimsey, 1952).

3. Kidney tumor occurs as one of the protean expressions of the gene for the von Hippel-Lindau syndrome and may be the only clinical expression.

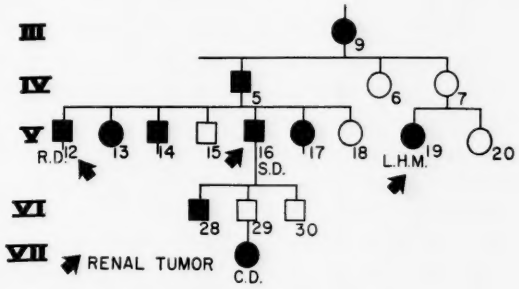

Fig. 71.—The von Hippel-Lindau syndrome with hypernephroma. In the large kindred affected by the von Hippel-Lindau syndrome reported from the Johns Hopkins Hospital by Silver (J.A.M.A. 156:1053, 1954), we know that at least 3 cases of "hypernephroma" have occurred:

1. L. H. M. (V 19) was operated on in 1922 at the age of 31 years for hemangioma of the cerebellum. At the age of 50, she underwent surgical operation for hypernephroma of the left kidney. She died 6 months after operation, presumably of metastases of the renal tumor. Hypernephroma was given as the cause of death on the certificate. There is no autopsy confirmation of the cause of death, however.

2. R. D. (V 12) developed signs of a left renal tumor at the age of 44 years. He was polycythemic despite considerable urinary bleeding (RBC 6.4 million). Surgical procedures were not performed. However, the diagnosis of "carcinoma of the kidney" was made on the basis of a filling defect in pyelograms. The patient died 7 months after first diagnosis. Autopsy was not performed. On the death certificate, the cause was listed as carcinoma of the kidney with carcinoma of the brain as a contributing factor. The patient had had severe headaches for about 4 months before death.

3. S. D. (V 16), who was asymptomatic at the time of Silver's report and who appeared therefore to represent a skipped generation (a son and more recently a granddaughter have shown signs), developed symptoms of a left kidney tumor which was removed in 1957 with a histologic diagnosis of hypernephroma. Since then the patient has remained well, without evidence of metastases. (Histologic sections were examined through the courtesy of Dr. Grover B. Swoyer, Charleston, W. Va.)

(Courtesy of Dr. Maurice L. Silver, Providence, R. I.)

4. The kidney tumors in the von Hippel-Lindau syndrome are more often than not designated as hypernephroma by the pathologist (Fig. 71).

5. The hemangioblastoma of the cerebellum in the von Hippel-Lindau syndrome presents a histologic condition closely resembling hypernephroma (Silver and Hennigar, 1952). Shown as an "unknown," sections of such tumors are likely to be diagnosed hypernephroma. The knowledge that the source is the posterior fossa suggests metastasis to the pathologist.

6. Vascularity of the "hypernephromas" which are accompanied by polycythemia is often striking.

7. Only a small proportion of all "hypernephromas" are accompanied by polycythemia.

All cases of renal tumor with polycythemia should be scrutinized for stigmata of the von Hippel-Lindau syndrome (retinal angiomatosis and cerebellar or spinal signs) and inquiry made as to the possible occurrence of this syndrome in the family. Most of the patients with polycythemic cases of hypernephroma have had metastases. Whether the kidney tumor of the von Hippel-Lindau syndrome metastasizes is not clear but seems likely. (See Fig. 71 for an example of a family with the von Hippel-Lindau syndrome and multiple cases of hypernephroma.)

XXIV. MISCELLANEOUS

940. In 4 affected members of a family with *hereditary angioneurotic edema*, Spaulding found that small daily doses of methyltestosterone prevented attacks. In 3 patients, attacks reappeared during placebo periods in the double blind study. The use of the agent was suggested by an associate, Bensley, who had found testosterone protects male guinea pigs from some effects of histamine.

Landerman, Becker, and Ratcliffe demonstrated an increased cutaneous response to diluted autologous serum in a patient with hereditary angioneurotic edema. The technique used consisted of the intravenous injection of Evans blue dye, 0.5 mg. per kilogram of body weight, followed in 5 minutes by the intradermal injection of serum. The intensity and size of the area becoming blue at the injection site at 30 minutes was observed as a gauge of an effect on vascular permeability. The patient's undiluted serum had no effect in the patient or in others. Diluted serum of the patient caused increased permeability in the patient but not in others. These workers postulated that hereditary angioneurotic edema is an inherited hyperresponsiveness of skin and other tissues to serum factor which is activated in vivo by unknown factors.

From experience in 5 cases in one family, 2 of them fatal, Richards and Crombie pointed out that the trauma of dental extractions can trigger off edema in the upper airways which may be fatal. The asphyxiating episodes occurred in the next 24 hours.

941. Albrecht studied the families of 224 persons with *bronchial asthma* and/or *pollen rhinitis*. He found no relation between age of onset and family history. Bronchial asthma and childhood eczema occurred more frequently in

males. Pollen rhinitis occurred equally in the sexes. No evidence of independent inheritance of asthma, rhinitis, and eczema was discovered. Irregular dominant inheritance was proposed.

Schnyder reported on a genetic study of neurodermatitis (atopic dermatitis), asthma, and rhinitis. The results have been previously reviewed (¶642).

942. In 8 patients with *familial Mediterranean fever*, Mellinkoff, Schwabe, and Lawrence discovered that a 20 Gm. fat diet greatly reduced the incidence of attacks. Shahin, Sohar, and Dalith and also Eyler, Nixon, and Priest described the roentgenologic findings in familial Mediterranean fever. Nixon and Priest reported 2 cases, one in an Arab male and one in a Jewish female. The simulation of acute surgical conditions of the abdomen was emphasized.

Fox and Morrelli observed a 27-year-old man of Dutch extraction who for 12 years had suffered from recurrent attacks of arthralgia, abdominal pain, and fever ("Mediterranean fever"). There was no family history of a similar condition. The patient died of renal insufficiency. Postmortem examination revealed amyloidosis of the kidneys, spleen, and adrenal glands.

Gafni and Sohar concluded that rectal biopsy is the most efficacious way to establish the diagnosis of amyloidosis in familial Mediterranean fever.

943. With Sallmann as moderator at a clinical staff conference at the National Institutes of Health, *primary amyloidosis* was discussed, with particular reference to the familial type.

Jackson and colleagues concluded that primary systemic amyloidosis is inherited as an autosomal dominant trait. They conclude that the α_2 globulin abnormality previously described is not a consistent finding of primary systemic amyloidosis and that elevation of serum hexosamine, which is found in nonhereditary primary amyloidosis, does not occur in the hereditary form. Urinary excretion of acid mucopolysaccharide is also within normal limits.

944. Williams and Campbell described 5 childhood cases of generalized *bronchiectasis* which, from radiologic and necropsy evidence, they suggested may be based on a congenital deficiency of cartilage in the bronchial tree.

Wier reviewed congenital anomalies of the lung. Those which have genetic interest include pulmonary arteriovenous fistulas and Kartagener's syndrome.

Gregory's familial data gave no support to the view of a hereditary predisposition to alcoholism. At least the occurrence of alcoholism in these families did not occur in a random manner, as one would expect if genetic factors were paramount, but was dependent on birth order and family size. The genetic hypothesis, while not supported, is not contradicted.

Knox, Murray, and Strang reported a sibship in which 2 members had both situs inversus and bronchiectasis (the *Kartagener syndrome*), while 2 others had only the bronchial abnormality. Linkage with the Rh locus was suggested by the fact that all 4 children with the syndrome got also a cde gene from the mother, whereas the one normal child received the other Rh gene, cDE. The father was homozygous cde.

Leites and Tannenbaum described 3 brothers who had had repeated *spontaneous pneumothorax*. Subpleural blebs were discovered in all 3. Deaf-mutism was present in 2 of the 3. A third brother was a deaf-mute but did not suffer from pneumothorax. One of the patients with spontaneous pneumothorax had severe pectus excavatum, a feature which suggests the Marfan syndrome, in which spontaneous pneumothorax also occurs.

945. Katz and Kunofsky studied *tuberculosis* in the patients of New York State mental institutions. They could demonstrate between white persons and Negroes no difference in the rate of development of the disease, the proportion of those with the disease who died, or the response to microbial drugs.

946. Belknap and Hayes studied the family distribution of *leprosy* in seven adjacent Roman Catholic parishes of southeastern Louisiana. The familial aggregation was consistent with determination of susceptibility by a single dominant gene with about 62.8 per cent penetrance. About one in every 20,397 births was susceptible, giving a gene frequency of about one in 40,794. The occurrence of leprosy in New Brunswick and in Louisiana among peoples of common Acadian origin has been a matter of interest and may indicate a genetic factor in susceptibility, although interpretation of familial aggregation of an infectious disease in simple Mendelian terms is hazardous.

947. Merchant and Utz observed *sarcoidosis* in a mother and daughter. Baer described sarcoidosis in 4 and possibly a fifth of 12 siblings in a Negro family. The family had moved to the San Francisco Bay area from southeastern Oklahoma and northeastern Texas. The family made a habit of chewing pine pitch.

948. In tissue cultures, Bang and Warwick demonstrated (1) cell specificity for pathogenicity of the mouse hepatitis virus and (2) genetic differences in cell susceptibility to the virus. The virus destroyed mouse macrophages but had no apparent effect on fibroblasts and epithelial cells. No destruction of macrophages from resistant strains of mice was observed. Tests of hybrids resulting from crosses between resistant and susceptible strains indicated that susceptibility is inherited. Segregation for susceptibility and resistance occurred in the f_2 and backcross generations. Segregation was evident in both the mice themselves and in the cultures derived from the mice. "The factor for susceptibility may be dominant, and possibly unifactorial, but further studies are necessary to establish this. The possibility that the tissue cultures from resistant mice are resistant because of latent infection in the mice themselves was examined and tentatively discarded."

949. Eysenck and colleagues found personality differences between *smokers and nonsmokers* and between pipe smokers and cigarette smokers and suggested that the findings are indicative of genotypic differences.

950. Ingold described a family in which *unilateral agalactia* (failure to secrete milk) was transmitted through four generations.

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